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Real-world evidence on the use and practice of electroconvulsive therapy at a Portuguese general hospital

Dissertação para obtenção do Grau de Mestre em Medicina

Orientador: Doutor Amílcar Silva dos Santos

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To Maria,
for blessing me
with her wisdom
and friendship

List of Scientific Publications

Silva-Dos-Santos, A., Venda, D., Sales, M.B., Velho, M.V., Gracias, M.J. (2021) 'Bottom-up neuroanatomical pattern of symptom remission in melancholic depression after electroconvulsive therapy: a case report and literature review', *Psychogeriatrics*, 21(2): 252-254. doi: 10.1111/psyg.12654 — reproduced with permission from the publisher.

Silva-dos-Santos, A., Sales, M., Venda, D. (2021) 'Symptomatic improvement of acute mania associated with a single session of electroconvulsive therapy: a proposed concept of neuroversion', *Bipolar Disorders*, Epub ahead of print. doi: 10.1111/bdi.13107 — reproduced with permission from the publisher.

«Telling people I've had ECT is a real conversation killer. People seem to be more forthright these days about discussing depression. Things have loosened up, even talking about medicine. Hell, the cashier in the grocery store told me yesterday that she's on Prozac. But ECT is in a different class. For months, in my conversations with most people, I have glossed over ECT's contribution to the end of my depression. But lately I've been thinking, "Damn it. I didn't rob a bank. I didn't kill anybody. I have nothing to be ashamed of." I've started telling people about ECT. My admission is typically met with uncomfortable silences and abrupt shifts in topics.

An acquaintance at a party is outrage. "How could you let them do that to you?"

I bristle and answer, "I didn't let them to it to me. I asked them to do it."

"But why would you ever do that" she insists.

"Because I was trying to save my life", I answer, hoping this will end the conversation.

Emboldened by a couple of bourbons, she challenges, "Aren't you being just a bit dramatic? Depression is hardly a life-and-death condition."

[…]

Nobody bats an eye when electricity is delivered to a stalled heart. There is not outcry. In fact, it's considered a miracle. A person passes from life to death to life again through the application of electric current do the heart. But try talking about the same thing with the brain, and it's no miracle. Suddenly, words like *torture* and *mind control* populate the descriptions.

I'm not about to stand on street corners urging people to try electroconvulsive treatment. […] But damn it, it worked. I didn't want to have it. Who would? I didn't want to have a caesarean section either. I ended up with a terrible infection, a long scar, and a difficult recovery. But I got Keara. A beautiful healthy new life. It was no picnic. But I'd do it again in a heartbeat.»

Undercurrents: a life beneath the surface,
Martha Manning (1995)

RESUMO

Introdução

A eletroconvulsivoterapia (ECT) modificada é fruto do que a medicina baseada na evidência é capaz de alcançar. As diretrizes internacionais posicionam-na como o tratamento padrão-ouro para condições psiquiátricas bem definidas, incluindo em doentes geriátricos e naqueles não responsivos ao tratamento habitual. Uma publicação recente sugere que a ECT é subutilizada em Portugal, país cuja prevalência de doença mental severa se encontra bem documentada. No entanto, não existe evidência disponível sobre o uso e a prática de ECT na prática clínica do mundo real, neste país.

Objetivos

Caracterizar o uso e a prática de ECT no Hospital de Vila Franca de Xira (HVFX), em Portugal, com particular enfoque nos desafios apresentados pela população geriátrica.

Métodos

Foi realizada uma revisão narrativa sobre a eficácia da ECT na população geriátrica com depressão unipolar resistente ao tratamento. Seguiu-se um estudo de investigação observacional, transversal e retrospetivo que incluiu os doentes tratados com ECT no HVFX, de 2018 a maio de 2021, após aprovação pela comissão de ética. Considerou-se o último tratamento de fase aguda, administrado em regime de internamento ou em ambulatório. Os doentes com processos clínicos incompletos (n = 2) ou abandono precoce do tratamento (< 4 sessões consecutivas, n = 6) e uma doente crónica refratária não-responsiva foram excluídos. Colheram-se variáveis sociodemográficas, clínicas e relacionadas com o curso de ECT a partir dos registos clínicos eletrónicos dos doentes elegíveis (n = 18). Estimou-se a taxa de prevalência de ECT entre os doentes internados (iP%). Foi conduzida uma análise descritiva comparando os doentes jovens (18-59 anos) e idosos (≥ 60 anos). Entrevistou-se o coordenador da unidade de ECT visando a identificação de barreiras locais no acesso a este tratamento. Por fim, descreveram-se três casos clínicos selecionados entre a subpopulação geriátrica (dois de depressão *major* e um de perturbação bipolar), a fim de ilustrar desafios diagnósticos, dilemas clínicos e achados de interesse.

Resultados

A idade média da amostra em estudo foi de 49,8 anos; 44,4% (n = 8) dos doentes pertenciam à faixa etária geriátrica. O diagnóstico mais frequente foi o de perturbação bipolar (n = 9; 50%), à custa dos episódios depressivos, seguindo-se depressão *major* (n = 6; 33,3%). A resposta inadequada a múltiplos ciclos farmacológicos constituiu a indicação mais comum (n = 9; 50%). A ECT foi iniciada com elétrodos em colocação bifrontal e pulso (ultra)breve. Verificou-se remissão em 60% (6/10) dos indivíduos jovens e em aproximadamente 88% (7/8) dos idosos. A mediana do número de sessões de ECT até à remissão foi de 4,0. Todos os efeitos adversos documentados foram transitórios e ligeiros, sendo os do foro cardiovascular os mais comuns. Durante o *follow-up*, objetivou-se recidiva ou recorrência em 25% (2/8) dos doentes jovens e em 37,5% (3/8) dos idosos. O iP% global foi de 1,9% (2,5% no período pré-pandémico e 4,0% no primeiro ano de atividade da Unidade de ECT). Entre as principais barreiras à provisão de ECT constam a falta de anestesiologistas, limitações de espaço e atitudes negativas em relação à ECT, seja por parte dos doentes ou dos profissionais de saúde.

Limitações

A reduzida dimensão da amostra e a quantidade/qualidade de informação documentada representam limitações importantes.

Conclusão

Esta tese fornece evidência empírica que suporta a ECT como um tratamento extraordinariamente eficaz, com ação rápida e bom perfil de tolerância, assumindo assim especial relevo na população geriátrica não responsiva ao tratamento farmacológico. Estes resultados, que estão de acordo com a evidência científica, devem encorajar o seu recurso como tratamento de primeira linha nos pacientes para os quais está indicada. Mais preocupante, contudo, é o uso subótimo da ECT, severamente limitado por razões não clínicas. No futuro serão necessários esforços colaborativos para colocar a ECT no lugar que merece: ao alcance dos doentes que dela beneficiam.

Palavras-chave

Eletroconvulsivoterapia · ECT · Idoso · Depressão resistente ao tratamento · Evidência do mundo real · Estudo observacional · Portugal

ABSTRACT

Background

Modified electroconvulsive therapy (ECT) stands as a sophisticated result of what evidence-based medicine can achieve. In international guidelines, it poses as the gold-standard treatment for well-defined psychiatric conditions, including in vulnerable patients such as the elderly and in those not responsive to treatment as usual. A recently published study points toward the underuse of this treatment in Portugal, a country where the prevalence of severe mental illness is well documented. However, the use and practice of ECT is yet to be assessed in this country, in a real-world clinical setting.

Objectives

The overall aim of this thesis was to characterize the real-world use and practice of ECT at Hospital Vila Franca de Xira (HVFX), in Portugal, with particular attention to the challenges presented by the geriatric population.

Methods

A literature review was performed on the efficacy of ECT for elderly patients with treatment-resistant depression. This provided a basis for a retrospective cross-sectional observational study conducted at HVFX, which included patients treated with ECT from 2018 to May 2021. Approval was obtained from the local ethics committee. The index treatment was defined as the last acute-phase course, whether inpatient or outpatient. Patients with missing data within the medical record (n = 2), early dropouts (< 4 consecutive ECT treatments, n = 6), and a chronic nonresponsive patient were excluded. Sociodemographic, clinical, and ECT-related variables were collected from the electronic medical records for all eligible patients (n = 18). An estimate of the inpatient ECT prevalence rate (iP%) was obtained. A descriptive analysis comparing the younger (18-59 years) and the geriatric group (≥ 60 years) was conducted. An informal interview with the ECT psychiatrist was conducted to identify local barriers to the use of ECT. Three case reports from selected geriatric patients (two regarding major depression and one about bipolar mania) were presented to illustrate further diagnostic challenges, often-competing forces, and serendipitous findings of clinical interest related to the index course of ECT.

Results

The mean age of the patient sample was 49.8 years; 44.4% (n = 8) were aged 60 years and older. The most frequent diagnosis was bipolar disorder (n = 9; 50%), at the expense of depressive episodes, followed by major depressive disorder (n = 6; 33.3%). A history of failed medication trials constituted the most common indication (n = 9; 50%). ECT was started with bifrontal electrode placement and (ultra-)brief pulse. Remission occurred in 60.0% (6/10) of younger subjects and in approximately 88% (7/8) of the elderly. The median number of ECT sessions to remission was 4.0. Only transient and mild adverse effects were reported, with cardiovascular adverse effects being the most common. At follow-up, 25% (2/8) of the younger subjects and 37.5% (3/8) of the elderly patients had an episode of relapse or recurrence. The overall iP% for the study period was 1.9% (2.5% in the pre-pandemic period; 4.0% on the first year of activity of the ECT unit). The main barriers to providing ECT included a shortage of anaesthesiologists, space limitations, and negative attitudes toward ECT held by patients and healthcare professionals.

Limitations

The small sample size and the amount of information retrievable represent major limitations of this retrospective chart review.

Conclusion

This thesis provides real-world evidence in support that ECT is a highly effective, rapidly acting, and well-tolerated treatment, thereby taking on special importance among geriatric patients exposed to multiple unsuccessful medication trials. These findings, in agreement with the scientific evidence, are reassuring and encourage the use of ECT as a first-line treatment in patients for whom it is indicated. What is worrisome is the suboptimal use of ECT, constrained by nonclinical reasons. Collaborative efforts are needed to place ECT where it should be: within reach for those in need.

Keywords

Electroconvulsive therapy · ECT · Aged · Treatment resistant depression · Real-world evidence · Observational study · Portugal

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List of Abbreviations

ECT	Electroconvulsive Therapy
HVFX	Hospital de Vila Franca de Xira
iP%	Inpatient ECT Prevalence Rate
MDD	Major Depressive Disorder
PMD	Psychotic Major Depression
TRD	Treatment-resistant unipolar depression

Chapter 1

Introduction

1.1 Context

There is sound scientific evidence favouring electroconvulsive therapy (ECT) as the most effective treatment for individuals with severe and/or treatment-resistant mood and psychotic disorders, both in the speed of remission and in remission rate (American Psychiatric Association, 2001). Modified ECT became standard practice, and the procedure has been further enhanced in such a way that, currently, it is one of the safest and well-tolerated medical procedures performed under anaesthesia, with minimal cognitive adverse effects (Roose and Sackeim, 2004; Tørring *et al*., 2017). International practice guidelines, that aim to ensure the minimum standards of care in ECT practice, established this procedure as a first-line treatment for a number of psychiatric conditions, especially in treatment-resistant or psychotic depression, catatonia, and severe suicidality (American Psychiatric Association, 2001; Bauer *et al*., 2013; Milev *et al*., 2016; Ferrier and Waite, 2019; Malhi *et al*., 2021). On top of this, ECT has also emerged as a cost-effective treatment option associated with positive long-term outcomes, including improved quality of life, decreased suicidality and all-cause mortality (Roose and Sackeim, 2004; McCall *et al*., 2018; Ross, Zivin and Maixner, 2018). From a scientific point of view, it would therefore be expectable that ECT has become a broadly available treatment in psychiatric units. However, that would be neglecting what is perhaps the only consensual fact about ECT: it carries a history of heated controversy that has raged unabated and remains as polarised as in the past.

Major international reviews concerning the contemporary practice of ECT have reported significant variations between and within countries, not only with respect to rates of use but also to clinical indications for referral, technical parameters, and legal provisions (Leiknes, Schweder and Høie, 2012; Lesage *et al*., 2016). It is puzzling that ECT remains seriously underused on a worldwide scale, with less than half of all psychiatric services within the same country assuring access to this treatment (Lesage *et al*., 2016; Patel *et al*., 2019). In the United States (US), the number of hospitalisations involving ECT delivery from 1993 to 2009 fell sharply, and mostly, for the geriatric population, with only 10.6% of general hospitals offering ECT as an inpatient procedure in the last year of the study period (Case *et al*., 2013). Between 2015 and 2017, Slade *et al*. (2017) investigated the entire population of psychiatric patients from US general hospitals in 9 states to find that only 1.5% of inpatients with severe mood disorders underwent ECT during their index hospitalisation. Recently, a population-based meta-analysis (n = 18), across 12 countries from the North American, European, Asian and Australian continents, identified a composite event rate of 17 people receiving ECT per 100,000 inhabitants, and confirmed a general trend toward the decrease of ECT provision over time, from 1973 to 2013 (Lesage *et al*., 2016).

In Europe, a previous review demonstrated an overall low use of ECT, provided by only 23% to 51% of all psychiatric units (Leiknes, Schweder and Høie, 2012). Whereas the Scandinavian countries display moderate to high rates of ECT use, and psychiatric institutions may have waiting lists for the administration of ECT (Schweder *et al*., 2011; Bjørnshauge, Hjerrild and Videbech, 2019), this practice is severely restricted in East European countries (Leiknes, Schweder and Høie, 2012; Gazdag *et al*., 2017). In Slovenia it was abolished altogether from 1994 onward (Gazdag *et al*., 2017). Large national and regional disparities have been reported in Western Europe as well, even in countries whose socioeconomic status is comparable (Sienaert and van den Broek, 2009). ECT is not available at all in

Luxembourg and is banned in the Swiss Canton of Geneva, meaning that patients referred for ECT need to be transferred to neighbouring countries (Felthous, 2009; Gazdag *et al*., 2012) – but what happens to such patients is another question. In Italy, where Cerletti and Bini first used ECT in a human patient as a psychiatric treatment, its provision is almost extinct today (Buccelli *et al*., 2016; Cattaneo *et al*., 2020). In Spain, despite the high proportion of facilities equipped with ECT, the rate of use of this treatment is paradoxically among the lowest in Western countries, having increased residually from 2000 to 2012. Further, in the units not performing ECT, available data suggests that it is considered merely 'the last hope' (Sanz-Fuentenebro *et al*., 2017). This latter finding is consistent with the results of van der Wurff *et al*. (2004), who conducted a postal questionnaire survey in the Netherlands addressed to geriatric psychiatrists (n = 91). Only a small part worked in appropriately equipped facilities or had performed ECT themselves (30.8% and 19.8%, respectively). The majority of the respondents considered ECT to be effective, safe, and acceptable in depressed elderly patients. However, they were overall much more reserved in their attitudes toward the use of ECT and diverted from the current national guidelines. In fact, only a minority would consider ECT as a first-line treatment in depressive disorder with psychotic features (15.1%), severe suicidal behaviour (13.9%), or severe physical exhaustion (25%), and remained reluctant even after two medication trials have been deemed unsuccessful. Similarly, only a small number considered that ECT should be applied in a depressive disorder with concomitant cerebrovascular disorders (23.4%) or Parkinson's disease (28.9%), even after two unsuccessful trials.

In this body of literature, two major conclusions stand out very clearly. First, nationally and internationally established guidelines have failed to harmonize the current practice of ECT (van der Wurff *et al*., 2004; Leiknes, Schweder and Høie, 2012). Second, ECT is offered only to a minority of the patient population for whom it is indicated, thus jeopardizing the quality of care of critical patients (Lesage *et al*., 2016; Sackeim, 2017). In this context, a question emerges: what is it about ECT that is hindering its use?

A myriad of professional, sociopolitical, and legislative barriers have been put forth to explain the insufficient implementation of ECT evidence-based practice. This would indeed deserve a separate study, and is discussed more fully elsewhere (Felthous, 2009; Royal College of Psychiatrists, 2019). Some of the professional barriers relate to the lack of infrastructure, proper funding, and specialist staff, either because of the underrepresentation of ECT in the curriculum for the Psychiatry residency or the lack of availability of trained anaesthesiologists to participate in ECT provision (Philpot *et al*., 2002; Reid, 2009). As noted by several authors, however, the remarkably low and uneven rates of ECT use are mostly anchored at political or ideological factors that cannot, today, be scientifically validated. A postal survey carried out in 23 European countries determined that the lack of patient access to ECT mirrored financial and other resource constraints, but above all political or legal pressures (Philpot *et al*., 2002). The pervasive stigma attached to ECT in the social imagery is historically rooted in decades of abusive use, misinformation, and abhorrent portrayals of 'true stories' in the cinema and other media, virtually devoid of scientific foundations in the light of current knowledge and practice (Felthous, 2009). On the other hand, the biological basis of psychiatric disorders has been often neglected in favour of psychological contributors, which once again discredits ECT as a legitimate and vital medical treatment (van der Wurff *et al*., 2004; Cattaneo *et al*., 2020). An inherent paradox stems from the fact that, contrary to the expectations, not even mental health professionals are excused from holding negative beliefs toward ECT (Reid, 2009; Leiknes, Schweder and Høie, 2012). Among psychiatrists, the perpetuation of fear and hostility associated with this treatment is likely to result in the discarding of ECT from the repertoire of viable treatment options and goes against the urging need to reduce the treatment gap in the delivery of mental health care to the patients most in need (Reid, 2009; Ferrier and Waite, 2019; Patel *et al*., 2019). It is the anguish, the stigma directed at, and the burden of people living with a severe mental health disorder that must come down, rather than ECT. Strict legal regulations,

imposed by sociopolitical forces, also affect to a great extent the use and accessibility of ECT, as has been blatantly criticised (van der Wurff *et al*., 2004; Cattaneo *et al*., 2020). The practice of ECT has been subjected to regulatory legislations inconceivable for other standard treatments, for which contributes the scepticism that continues to be fuelled by a vocal antipsychiatry movement (Felthous, 2009). The most recent request for the radical abolishment of ECT was led by a team of anti-ECT psychologists in the United Kingdom (Read, Kirsch and McGrath, 2019). In the press release, the lead author stated that their aim would be «to finally put an end to this well-intentioned but calamitous error in the history of medicine» (University of East London, 2020).

1.2 Problem Statement

The Portugal National Mental Health Survey – 1st Report, conducted by Caldas de Almeida *et al*. (2013) was the first to provide population-representative data about the prevalence and the correlates of mental disorders in our country. Overseen by the World Health Organisation and Harvard University, this study was part of an international project, the World Mental Health Survey Initiative, aiming to assemble a large cross-national dataset on the epidemiology of mental illnesses throughout the world (Caldas de Almeida *et al*., 2013).

The results of this report revealed that Portugal is one of the countries with the highest prevalence of mental illnesses (22.9%) in all diagnostic groups, only surpassed by a small margin by Northern Ireland (23.1%) and the US (26.4%). For reasons that are not yet clear, Portugal is at a much higher level than other Southern European countries, where the prevalence of mental illnesses were comprised between 8.2% and 11.2%. With regard to the degree of severity, 17.5% of the number of psychiatric cases correspond to a severe psychiatric disorder, which accounts for 4% of the Portuguese adult population. These data are especially worrisome considering the resulting burden: in Portugal, mental disorders are the leading cause of years lived with disability (YLDs) and the second cause of disability-adjusted life years (DALYs) lost, falling behind cerebrovascular diseases but ahead of cancer (Direção-Geral da Saúde, 2016). Another indicator that captures the severity of mental illness is the death rates from suicide. Although slowly declining, the registered suicide rates in Portugal are the highest in Southern Europe (Gusmão *et al*., 2021). Notwithstanding the considerable prevalence of severe psychiatric morbidity and mortality in Portugal, and the international validation of ECT as the gold-standard treatment for a number of such disorders, data on the use and practice of ECT in the national setting did not exist until a few years ago (Sienaert and van den Broek, 2009). Fortunately, a few publications have flourished in recent years.

In 2008, following a well-attended national conference on ECT, a group of Portuguese psychiatrists formed the *Sociedade Portuguesa de Eletroconvulsivoterapia*, a Portuguese association for dissemination of and research on ECT, chaired by Doctor António Gamito (Sienaert and van den Broek, 2009). According to the information provided directly by Doctor António Gamito (president) and Doctor Jorge Mota (vice president), this association promoted, among other activities, the First National Neurostimulation Meeting in 2019. As part of this, the Society's vice president, Doctor Jorge Mota, published a science book on the history, the technical principles, and the therapeutic effects of ECT (Mota, 2019). Unfortunately, due to logistical issues and the Covid-19 pandemic, the association has not been as active as expected.

The first and only Portuguese nationwide, register-based study on ECT was recently undertaken by joint action of the Porto Medical School, CINTESIS – Health Technologies and Services Research Centre, and the Tâmega and Sousa Hospital Centre (Mota *et al*., 2021). Mota and colleagues covered all ECT-related psychiatric hospitalisations in public hospitals over an 8-year period (2008-2015),

amounting to a total of 879 registered hospitalisations to 674 unique patients. The number of hospitalisations per year, ranging between 85 and 150, peaked in 2013 and has decreased since then (Figure 1). Patient's mean age increased in the last three years of the study period, with a 56.5-year-old average in 2015. Major depression was the most frequent diagnosis, followed by bipolar I disorder. During the study period, 0.71% of inpatients received ECT, which places Portugal among the European countries with a lower rate of ECT provision, between Hungary and Poland (Leiknes, Schweder and Høie, 2012; Lesage *et al*., 2016). This finding is consistent with unpublished data presented at a Portuguese national conference on ECT (Sienaert and van den Broek, 2009). A treated person rate of 0.5 to 1.2 patients per 10,000 resident population was reported in 2007, which is comparable to the ECT use at a rate of 0.66/10,000 in Spain, in 2012 (Sanz-Fuentenebro *et al*., 2017).

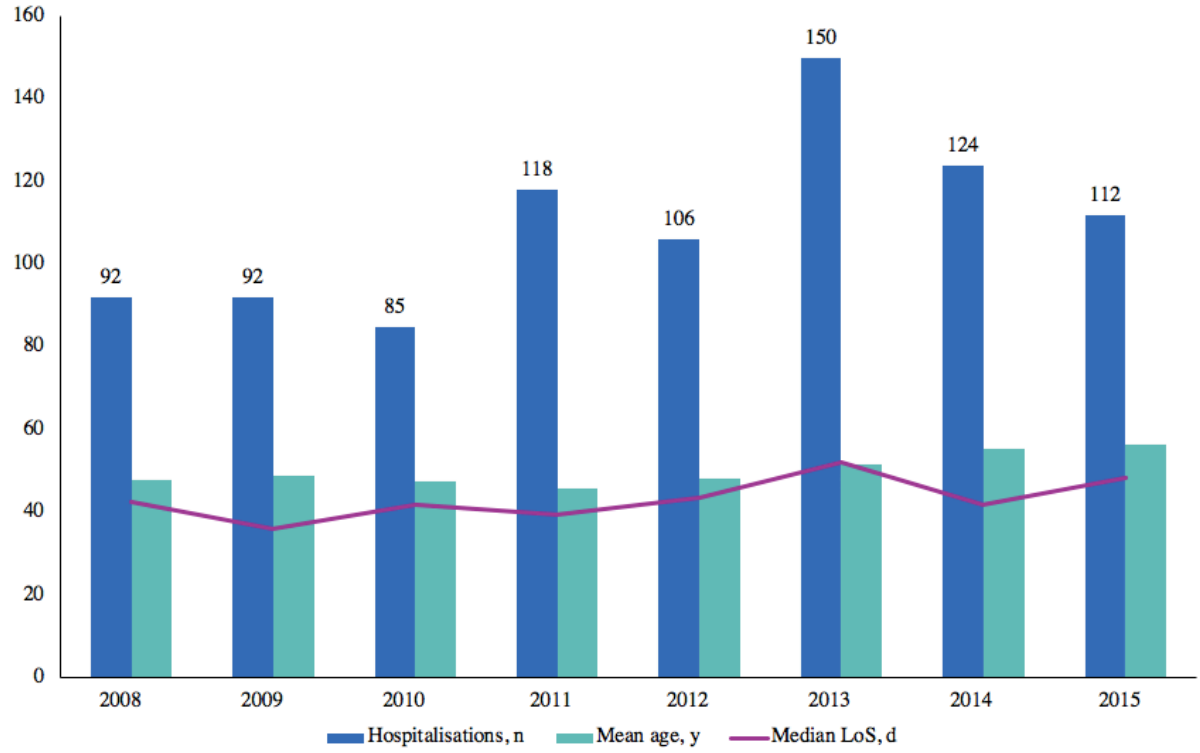


Figure 1. Trends in Portugal's psychiatric hospitalisations with the procedure code 94.27 ('Other electroshock therapy') [ICD-9-CM], from 2008 to 2015. LoS, length of stay.

Note. Adapted from Mota, P., Gonçalves-Pinho, M., Ribeiro, J.P., Macedo, S., Freitas, A., Mota, J. (2021) 'Electroconvulsive Therapy Use in Psychiatric Hospitalizations in Portugal: A Nationwide Descriptive Study', *The Journal of ECT*, Online ahead of print.

A questionnaire-based study of ECT practice in Portugal, retrieving data for 2017, seems to point in the same direction (Manique, 2019). The study found that, from all public psychiatric units (n = 43), only around one third can provide ECT, as illustrated below in Figure 2. It is of further concern that at least 11% neither applied nor prescribed ECT, a number that is close to the corresponding estimate of neighbouring Spain (15.8%) (Sanz-Fuentenebro *et al*., 2017).

The same study also reported wide regional variability in the use of this procedure, with only 5 of the 13 Portuguese regions having access to an ECT facility within their geographic area. Excluding the two main metropolitan areas of the country (Lisbon and Oporto), where ECT services were more prevalent, the prescription rate of ECT was lower than 10 patients per 100,000 inhabitants (Figure 3). Lamentably, only 65% (n = 28) of the surveyed institutions returned the questionnaires, which hampers further conclusions (Manique, 2019).

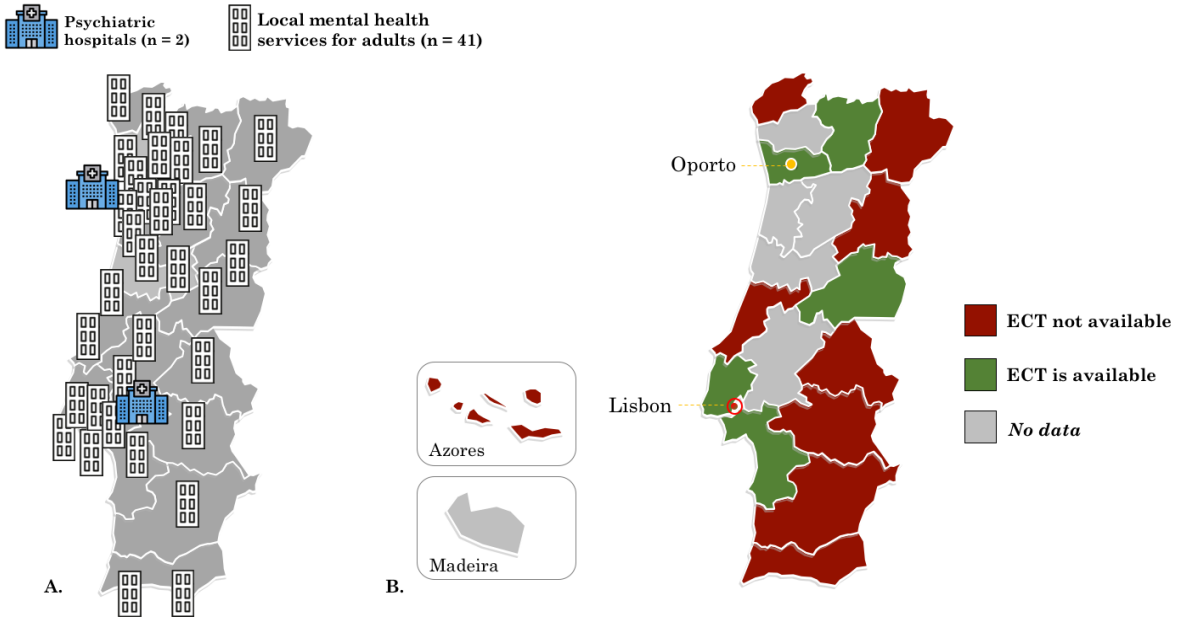


Figure 2. A. Adult mental health services throughout Portugal (adapted with permission from Direção-Geral da Saúde, 2017). B. Geographical accessibility of public ECT services in Portugal, by district, based on data from 2017.

Note. Adapted with permission from Manique, H. (2019) 'Padrões de Uso da Terapia Eletroconvulsiva em Portugal. MSc. Universidade da Beira Interior.

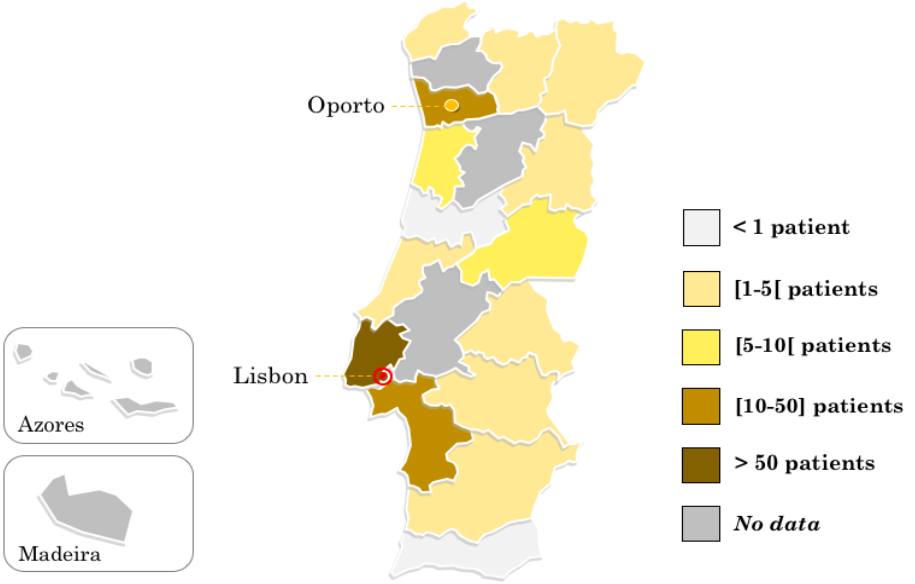


Figure 3. Rates of ECT use by district in Portugal, per 100,000 inhabitants, based on data from 2017 (adapted with permission from Manique, 2019).

1.3 Aims of the Thesis

The overall aim of the thesis was to characterize the use and practice of ECT in a Portuguese real-world setting, with particular attention to the challenges presented by the geriatric population. This was preceded by a literature review to set the context of research and further illustrated by reporting 3 elderly patients in whom treatment with ECT was required. The specific aims and research questions addressed in the individual studies were as follows:

Study I

Aims. To review the conceptual and operational criteria for treatment-resistant unipolar depression (TRD), as a means to then provide an overview of current evidence on the efficacy and safety of ECT in geriatric patients with TRD.

Research questions. How to operationalise treatment resistance in clinical practice? What is the place of ECT in current treatment algorithms for elderly patients with TRD? What is the influence of age on ECT outcome?

Study II

Aims. To establish a baseline understanding of the use and practice of ECT in Hospital de Vila Franca de Xira (HVFX) over the course of three years, with a major focus on comparing the sociodemographic, clinical, and ECT-related data between younger (18-59 years) and older (≥ 60 years) patients treated with a course of acute-phase ECT; to provide a crude estimate of the proportion of ECT-treated patients among the inpatient population (the inpatient ECT prevalence rate, iP%); and to identify possible barriers limiting access to ECT.

Research questions. How does the efficacy, safety/tolerability, and treatment outcomes of ECT in elderly patients compare with those in a younger age group? Where does the inpatient ECT prevalence rate at HVFX stand compared with national and international data? What are the major barriers restricting the timely delivery of ECT for whom it is indicated?

Study III

Aims. To describe the clinical presentation and differential diagnosis of a 63-year-old male in which catatonic and psychotic features were diagnosed at the background of major depressive disorder nonresponding to first-line treatment; to highlight the need for prompt identification and treatment of psychotic major depression, with an emphasis on inpatient management challenges and the role of acute ECT as a life-saving treatment.

Research questions. Why does the general population remain 'resistant' in considering ECT as a medical treatment? How does the time course of symptomatic remission of this individual patient fit into that reported for depressive patients treated with ECT?

Study IV

Aims. To report the case of a 69-year-old woman diagnosed with treatment-resistant major depression with melancholic and psychotic features, after being in a neuro-rehabilitation ward for over a year; to stress the importance of considering ECT earlier in the treatment protocol of severely ill patients with ECT-responsive conditions.

Research questions. How to interpret the temporal pattern of symptom improvement from a phylogenetic viewpoint?

Study V

Aims. To present the case of a 63-year-old woman diagnosed with psychotic mania who did not tolerate first-line pharmacological treatment and was therefore referred for ECT.

Research questions. How to explain the patient's symptomatic improvement after a single session of ECT that did not elicit seizure activity?

1.4 Significance

The process of healthcare improvement is cyclical by nature and must start with a comprehensive understanding of the state of the art, to measure current practice against standards (World Health Organization, 2006). The findings from the few studies available unveil a lack of standardisation of ECT practice and underuse of ECT in Portuguese psychiatric hospitals, possibly implying a treatment gap in the management of severe and/or treatment-resistant psychiatric disorders. Since the prevalence of severe mental illnesses in Portugal is high, it is crucial to reach a baseline understanding of the status of ECT in the real-life clinical practice setting. Addressing the current knowledge and treatment gaps in ECT provision might help developing mental health policies and strategic initiatives to ensure standardisation of high-quality and evidence-based mental health care.

Chapter 2

Literature Review

2.1 Methods

A literature review was performed on the conceptual and operational criteria for treatment-resistant unipolar depression (TRD), as a means to provide an overview of current evidence on the efficacy of ECT in geriatric patients with TRD. The need for this narrative review arose from several factors: first, the lack of consensus, both among clinicians and researchers, about what is and how to manage TRD; divergent views about the place of ECT in treatment algorithms; and the interest in a special population, the elderly, in whom evidence-based treatment algorithms are still lacking.

2.1.1 Literature search strategy

The search was conducted in March 2021. Studies were identified by searching three electronic databases: PubMed, Scopus, and Cochrane Central Database. Search terms utilised for recollection were as follows:

PubMed: (electroconvulsive* OR ECT) AND (“treatment resistan*” OR “drug resistan*”) AND (elderly OR older OR geriatric OR “late life”) AND (“major depressi*” OR “unipolar depression” OR melancholi*) NOT schizo*

Scopus: TITLE-ABS-KEY (electroconvulsive* OR ECT) AND TITLE-ABS-KEY ("treatment resistan*" OR "drug resistan*") AND TITLE-ABS-KEY (elderly OR older OR geriatric OR "late life") AND ("major depressi*" OR "unipolar depression" OR melancholi*) AND NOT schizo*

Cochrane Central Database: Electroconvulsive therapy AND elderly (in Title Abstract Keyword)

The author screened all articles. Additional articles were identified by a manual search through the reference lists of the eligible studies retrieved in the round of search. Official guidelines and textbooks on ECT were also included. The authors of the selected articles that could not be retrieved by a manual search were contacted. All search results were entered into the Mendeley reference manager for review and removal of duplicate citations.

2.1.1 Eligibility criteria

The exclusion criteria were as follows: early research with poor-quality data; articles for which full text was not available; non-English language articles; citations with content not relevant to the current review (including those focused on bipolar depression, the neurobiological effects of ECT, the influence of the genotype and anaesthetic agents on ECT outcomes).

2.2 Treatment-resistant unipolar depression

2.2.1 Prevalence of TRD

Despite no agreed-upon conceptual basis, treatment-resistant depression (henceforth TRD) is relatively common in clinical practice. However, no consistent data regarding its prevalence is currently available (Kubitz *et al*., 2014; Demyttenaere and van Duppen, 2019). The heterogeneity in diagnostics and assessment constructs of TRD has naturally resulted in a diverse range of prevalence estimates across clinical studies, varying from 6.6% (Kubitz *et al*., 2014) to 29% (Gibson *et al*., 2010), in two US commercial claims databases, while a Danish register-based study found a prevalence of 15% (Gronemann *et al*., 2021). Data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study indicate that only about half the patients reach remission after two treatment lines. After the four levels of treatment, assuming no dropouts, the theoretical cumulative remission rate did not surpass 67% (Rush *et al*., 2006; Rush, 2011).

A frequently quoted paper by Mulsant and Pollock (1998) reports the occurrence of TRD in up to one third of elderly depressed patients. Regrettably, geriatric-specific evidence remains sparse and, to my knowledge, no large study has systematically assessed the epidemiology of TRD in the geriatric population. It is reasonable to assume that prevalence rates of TRD may be higher in the elderly compared to younger patients, taking into account some of the age-related challenges that characterise this population (namely, greater comorbidity, higher medication intolerance, and possible drug-drug interactions) (Flint and Gagnon, 2002; Kerner and Prudic, 2014; Knöchel *et al*., 2015).

2.2.2 Challenges in defining TRD

Considering that major depression is a biologically heterogeneous syndrome, it should come as no surprise that there is no one-size-fits-all standard of care for depressed patients (Parker, 2000; Rush *et al*., 2006; Malhi *et al*., 2020). To compound the problem, what should constitute the desired treatment outcome is not unanimously accepted, and there is a striking lack of consensus, among both researchers and clinicians, related to the conceptual and operational definitions of 'treatment resistance' (Berlim and Turecki, 2007; Demyttenaere and van Duppen, 2019).

Full remission – that is, the absence of symptoms – has come to be regarded as the gold-standard outcome for antidepressant treatment, opposed to clinical improvement or response (Berlim and Turecki, 2007). The rationale for this approach builds on previous studies that have hinted substantially lower relapse rates among those patients who entered the follow-up phase in remission, irrespective of the number of treatment steps required (Rush, 2011). It should be remembered, however, that the classical definition of symptomatic remission does not equate to that of functional recovery, which in turn implies the resumption of the patient's normal functioning (Wijeratne and Sachdev, 2008; Malhi *et al*., 2020).

Differently from remission, the concept of TRD has been variably approached in a more categorical, as an all-or-nothing phenomenon, or dimensional way, as lying on a continuum (Demyttenaere and van Duppen, 2019; Johnston *et al*., 2019). The standard definition adopted by the European Medicines Agency posits treatment resistance as a categorical variable, objectifiable «when treatment with at least two different antidepressant agents […] showed lack of clinically meaningful improvement» (European Medicines Agency, 2013). However, current state-of-the-art evidence tends to regard TRD dimensionally rather than categorically, taking into account patient-, illness- and treatment-related factors (for a detailed review consult Parker *et al*., 2005; Fekadu *et al*., 2009; Demyttenaere and van Duppen, 2019).

Despite the ample and increasing amount of literature available, TRD remains, at most, an ill-defined concept whose translation into routine psychiatric practice is still a subject of debate. In a

systematic review of randomised trials (n = 47), Berlim and Turecki (2007) found eleven descriptive terms (including 'medication-resistant', 'treatment-refractory' or 'resistant') and six different sets of criteria, differing not only on the classes of antidepressants but also on the minimum number of failed trials and respective durations. A recent systematic review of the published literature (n = 152) identified as many as 155 definitions of TRD, which required a minimum number of failed trials varying from a single to more than five antidepressant treatments (Brown *et al*., 2019). Nevertheless, an empirically supported definition seems to be emerging within the specialised literature, whereby TRD refers to the failure to achieve full remission in patients with major depressive disorder (MDD) after at least two consecutive trials of antidepressant pharmacotherapy, given at adequate dose for an adequate length of time (Berlim and Turecki, 2007; Brown *et al*., 2019).

Such definition can be criticized on several grounds. On the one hand, this constrained approach neglects a number of variables, not primarily disease-related, that could account for some of the cases of 'pseudo-resistance', including unsystematic use of the available armoury of treatment options, patient noncompliance, poor tolerability to prescribed treatments, diagnostic inaccuracy, relevant psychiatric and/or somatic comorbidities (Flint, 2002; Bennabi *et al*., 2019; Kellner and Nordenskjöld, 2019). Interestingly, Parker and colleagues (2005) identified six of such 'paradigm failures' in a sample of outpatients with severe and/or treatment-resistant mood disorders (n = 164), suggesting that the prevalence of TRD is likely to be overestimated if these factors are not factored into clinical decision-making.

This argument is strengthened by ECT research literature. Data from a large, multisite study performed by the Consortium for Research on Electroconvulsive Therapy found that 63% of patients with nonpsychotic depression had received at least one inadequate trial of an antidepressant medication before referral for ECT (Rasmussen *et al*., 2006). Of added concern are the results of a prospective survey involving TRD patients referred for ECT (n = 37), in which only half of the sample met contemporary operationalised criteria for treatment resistance (Husain *et al*., 2005).

On the other hand, TRD is framed here as a homologous and unitary entity (Nemeroff, 2007) based solely on the number of sequential pharmacotherapy failures. This seems a nearly procrustean approach whereby TRD is fitted into an empirical category, especially given that its underlying aetiology and pathophysiological mechanisms remain elusive. Another caveat is that recent literature does not support the existence of 'degrees of resistance' defined by the number of failed treatment trials, as further discussed below. Therefore, the clinical utility of labelling patients 'treatment resistant' is rather questionable and potentially hazardous to the trialogue between physician, patient, and significant others (Parker *et al*., 2005; Wijeratne and Sachdev, 2008; Demyttenaere and van Duppen, 2019; Kellner and Nordenskjöld, 2019; Malhi *et al*., 2020).

In stark contrast with other medical fields, a tangible gap remains between real-world clinical practice and trial data on TRD (Malhi *et al*., 2021). As Bauer *et al*. (2019) provocatively concluded, in a review of algorithm-guided treatments for MDD, at least highly diligent management is not the usual treatment in today's clinical practice. This is indeed a huge unmet need in the treatment of mood disorders, and not restricted to later life (Ghio *et al*., 2014; Heerlein *et al*., 2021). Most current guidelines do not specifically target TRD patients and there is no robust guidance on the optimum next-step approaches once the first treatment trial fails (Macqueen *et al*., 2017; Bauer *et al*., 2019), which eventually leads to the implementation of treatment plans that may not always mirror evidence-based practice. The major impact of the problem is underlined by the demonstration that the more the number of treatment steps needed, the lower the likelihood of subsequent remission (Rush *et al*., 2006).

The limitations inherent to the conceptualisation and operationalisation of TRD fostered a recent consensus statement from an international group of experts (McAllister-Williams *et al*., 2020). The authors argued for an inclusive definition of 'difficult-to-treat depression' (DTD), which is defined as

«depression that continues to cause significant burden despite usual treatment efforts». Broadly speaking, compared with the concept of TRD, the DTD model encompasses a more chronic, holistic, and collaborative perspective in which depression is viewed as a treatable, instead of 'resistant', condition. Yet, both concepts pose some overlapping issues: the terminology itself invokes a nihilistic, potentially stigmatizing view (who/what is 'resistant' or 'difficult': the patient or the illness?), and misleadingly convey the idea that antidepressant treatments are highly effective, which has not been proved (Rush *et al*., 2006; Turner *et al*., 2008); both are impaired by broad diagnostic criteria, allowing for a questionable manageability in the clinical setting; and much of the emphasis is placed on non-response (Malhi *et al*., 2020). Additional implications of the DTD heuristic are discussed in greater detail elsewhere (Rush, Aaronson and Demyttenaere, 2019; McAllister-Williams *et al*., 2020).

Arguably, a more appealing (or rather, complementary) model in the management of depression is the one proposed by Malhi and colleagues. This model, translated into the Royal Australian and New Zealand College of Psychiatry clinical practice guidelines for depression (Malhi *et al*., 2021), shifts the primary focus towards treatment 'response' rather than 'poor response' or 'resistance', thus introducing a new concept – the channelling response (Malhi *et al*., 2020).

The fact that depression is an umbrella term covering multiple heterogeneous subtypes of variable severity cannot be overlooked. In the light of this paradigm, depression is then envisaged as a composite entity that will eventually respond to different treatment pathways (schematized in Figure 4 as 'channels of response'). As such, this perspective not only obviates the need for a non-response threshold, but also highlights the very many potential pathways that can be recruited throughout the management of depression, with a view to achieve the patient's recovery. As the authors put it, «different depressions comprise different responsivities and will therefore respond to different treatments» (Malhi *et al*., 2021), which evokes the disorder-treatment specificity or 'horses for courses' paradigm proposed by Parker *et al*. (2005). Importantly, by changing the narrative of 'treatment resistance' to 'responsiveness' this approach assists both patients and clinicians alike, while realistically addressing the challenges of real-world practice (Malhi *et al*., 2020).

The place of ECT in the hierarchy of treatment may serve as a good example to illustrate the so-termed 'channelling response paradigm': it may either be used secondarily, as part of a broader treatment scheme, in order for full remission to be attainable (Figure 4-E); but it may also be required from the outset in certain clinical pictures (Figure 4-F), including, but not limited to, major depression with superimposed psychotic and/or melancholic features. The authors gave the interesting example of delivering ECT after a course of serial treatment trials that proved to be unsuccessful, which frequently opens up the chances of good response to subsequent treatments, including the ones that previously did not elicit a clinical response (Malhi *et al*., 2021). Again, this calls into question why non-response to a number of antidepressant trials is equated to TRD in most contemporary definitions (Kellner and Nordenskjöld, 2019; Malhi *et al*., 2020).

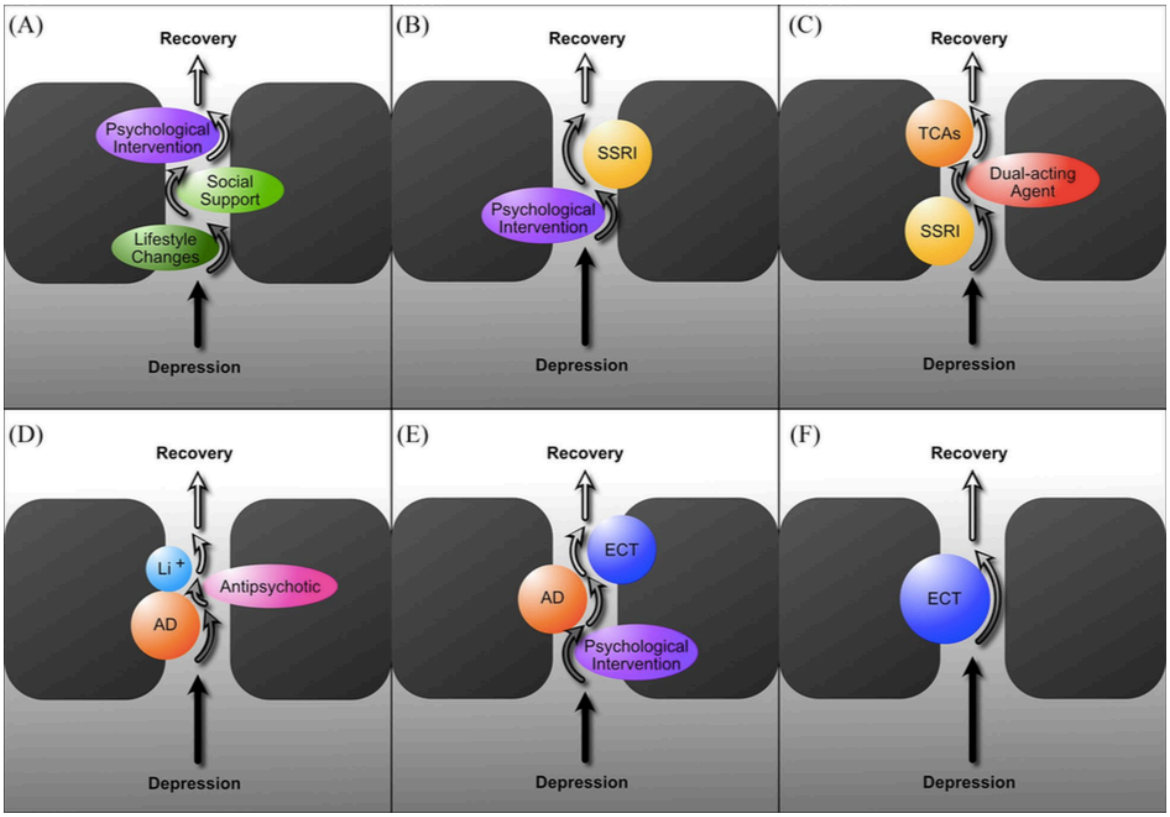


Figure 4. Schematic of the channelling response paradigm proposed by Malhi et al (2020). Different treatment pathways ('therapeutic channels of response') are represented to illustrate the patient's journey from a depressed mood state to functional recovery, including variable combinations of lifestyle changes, psychological interventions, pharmacotherapy, and ECT. The clinical response is depicted as arrows. (E) and (F) illustrate the possible role of ECT as a second- or first-line treatment, respectively, for the individual to meet full recovery.

Note. From Malhi, G.S., Bell, E., Bassett, D., et al. (2020): 'The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders', Australian & New Zealand Journal of Psychiatry, 55(1): 7-117. Reproduced with permission of the authors.

2.2.2 The burden of TRD

The burden attributable to TRD is substantial, rivalling that of other chronic conditions such as diabetes or cancer (Mrazek *et al*., 2014). In comparison with non-TRD, TRD has been reported to entail disproportionately higher personal, economic and societal burdens, including higher medical comorbidity, impaired functionality, higher healthcare costs, as well as lower health-related quality of life and increased premature mortality (Demyttenaere and van Duppen, 2019; Johnston *et al*., 2019), both in American (Mrazek *et al*., 2014) and in European settings (Heerlein *et al*., 2021). Hence, it could be hypothesized that the implementation of more vigorous treatments in earlier stages may, if successful, decrease the global economic, societal and humanistic burden of TRD.

2.3 Evidence base for ECT effectiveness

2.3.1 ECT in treatment guidelines

Guidelines from the five most authoritative psychiatric associations clearly establish ECT as a first-line treatment for all patients with major depressive disorder whose medical or psychiatric condition require rapid and/or definite response (American Psychiatric Association, 2001; Bauer *et al*., 2013; Milev *et al*., 2016; Royal College of Psychiatrists, 2019; Malhi *et al*., 2021). This category encompasses patients with psychotic features, catatonia, and/or in life-threatening situations (e.g., high suicide risk, food or fluid refusal). The preferred use of ECT in these circumstances is predicated on its efficacy and speed of action (see below). Moreover, most guidelines also recommend the primary use of ECT in cases of prior good response to this treatment modality and patient's preference (American Psychiatric Association, 2001; Bauer, Pfennig, Severus, Whybrow, Angst and Möller, 2013; Milev *et al*., 2016; Malhi *et al*., 2021).

ECT is generally regarded as a second-line treatment for patients with TRD. Curiously, most of these guidelines (American Psychiatric Association, 2001; NICE, 2009; Canadian Network for Mood and Anxiety Treatments, 2016) do no provide an explicit definition of TRD, and only a few offer specific guidance on treatment strategies (World Federation of Societies of Biological Psychiatry, 2013; The Royal Australian and New Zealand College of Psychiatrists, 2021). In particular, the Royal Australian and New Zealand College of Psychiatrists' guideline devotes one section to treatment response, placing emphasis on the paradigm shift from treatment 'resistance' to treatment 'responsivity', with a view to achieving functional recovery (Malhi *et al*., 2021). However, none of these guidelines present stepwise (algorithmic) treatment approaches, which have been recognized as key instruments to provide better outcomes in patients with MDD than treatment as usual (Bauer *et al*., 2019).

The aforementioned indications are valid irrespective of the patient age. Only the National Institute for Health and Care Excellence displayed some reserve on the use of ECT in the elderly, stating that «the risks associated with ECT may be greater in older people» and advocating «particular caution when considering ECT treatment in this group» (NICE, 2009). In contrast, the Royal College of Psychiatrists' position statement is more robust in its recommendations regarding the elderly (Royal College of Psychiatrists, 2017). Also, the Canadian Network for Mood and Anxiety Treatments (2016) state that «while special populations (older adults) bring unique challenges, the essential approach to depressive episodes is similar to that of the general adult population» (MacQueen *et al*., 2016). Of note, the authors devote a brief paragraph to the role of nonpharmacological treatments in late-life depression and an algorithmic pharmacological treatment is recommended, whereas there are no specific recommendations concerning ECT technique.

These serious shortcomings have been remedied, in part, by the formal consensus method, that aims at bridging the gap between empirical literature and real-world clinical practice (Bennabi *et al*., 2019; Agüera-Ortiz *et al*., 2020). The guidelines on late-life depression commissioned by the World Psychiatric Association (Baldwin *et al*., 2002) emphasize that «inadequate response to two trials of medication» is a formal indication for ECT, though «at any stage ECT may be the preferred option» in poorly responsive patients (strength-of-recommendation grade: C). Conversely, the French expert consensus guidelines on TRD state that «brain stimulation techniques should be reserved for situations of treatment resistance and recommended in the first intention, although only from the fourth line of treatment» (Bennabi *et al*., 2019). In the same line, a Delphi-based consensus on geriatric depression from the Spanish Psychogeriatric Association recognised that «ECT is the best therapeutic option when pharmacological treatment fails». Nonetheless, no agreement was reached «on the time required to assess refractoriness to pharmacological treatment prior to prescribing ECT, although the panel strongly

disagrees with prescribing ECT beyond 24 weeks from the described situation» (Agüera-Ortiz *et al*., 2020).

In sum, considering that TRD is one of the most common indications for ECT (Kellner, Obbels and Sienaert, 2020), particularly in elderly recipients (Roose and Sackeim, 2004), the dearth of systematic treatment strategies for elderly patients with TRD is particular disappointing and leaves much room for improvement. The inclusion of ECT in the treatment plan is often relegated as 'last resort' in widely used guidelines, after countless pharmacological treatments have been exhausted (Birkenhäger and van Diermen, 2020; Cattaneo *et al*., 2020; Kellner, Obbels and Sienaert, 2020). Admittedly, in everyday clinical practice, many practitioners do not consider ECT until they are 'out of options', depending on their own clinical experience and accessibility to the technique (Kellner and Nordenskjöld, 2019; Agüera-Ortiz *et al*., 2020; Cattaneo *et al*., 2020).

Why might this be so? Is it a downstream consequence of the fact that modern ECT technique is not good enough? The following sections will attempt to address this question.

2.3.2 Sham ECT studies

Randomised placebo-controlled trials are recognised as the gold-standard methodology in the evaluation of the effectiveness of a medical treatment, psychiatric or not, and ECT is no exception to that (Abrams, 2002; Rasmussen, 2009).

Previous reviews (Abrams, 2002; Rasmussen, 2009) and five meta-analysis (Janicak *et al*., 1985; Geddes *et al*., 2003; Kho *et al*., 2003; Pagnin *et al*., 2004; Mutz *et al*., 2019) all provide firm evidence of the superiority of (real) ECT in mixed-age populations compared with simulated or 'sham' ECT (that comprises all the components of the ECT procedure, including the anaesthesia, but with no electrical stimulation). In the aggregate, these results fuel the argument that the therapeutic efficacy of ECT is predicated on the passage of an electrical stimulus and/or the elicitation of a motor/electroencephalographic seizure (Roose and Sackeim, 2004).

Despite the proved superiority of active over sham ECT, a remarkably high placebo (that is, expectational) response in the sham ECT groups was also reported across studies, exceeding 30% in some trials (for a detailed review view Rasmussen, 2009). These results seem to be aligned with current evidence with regard to non-somatic treatments. In a review of 75 randomised, placebo-controlled trials of antidepressant medication for unipolar MDD, the placebo response was reported to be highly variable but often substantial, with half of the studies estimating it to be at least 30%, irrespective of patient's age (Walsh *et al*., 2002).

Taking this body of findings one step further, O'Leary *et al*. (1994) conducted a reexamination of data from the Nottingham randomised controlled trial (Gregory, Shawcross and Gill, 1985) and concluded that ECT is significantly more effective than simulated ECT in elderly depressed patients. Owning to the fact that this is the only controlled trial of real versus sham ECT in this age group, a Cochrane review concluded that the randomised evidence was too sparse to determine the efficacy of ECT in this population (Stek *et al*., 2003). However, subsequent reviews, which included the extensive nonrandomised literature, established the effectiveness of ECT in the acute treatment of major depression in elderly patients (Stek *et al*., 2003; Frazer, Christensen and Griffiths, 2005; Heijnen *et al*., 2010; Rhebergen *et al*., 2015; Geduldig and Kellner, 2016; Kellner *et al*., 2016a).

Notwithstanding, a recent meta-analysis performed by Read and colleagues has put a definite question mark against the efficacy of ECT in major depression, and the authors went so far as to call for a moratorium on ECT pending new randomised, placebo-controlled trials (Read, Kirsch and McGrath, 2019). This publication, sharply criticized by prominent ECT researchers and other practitioners (for a more extensive analysis consult Cattaneo *et al*. (2020); Goldberg, 2021), is likely to mirror the broader antipsychiatry movement and deserves, in my opinion, a few observations.

The meta-analysis in point includes data from 11 small trials (average number of patients: 37) comparing ECT with a sham intervention (SECT). The authors argue that «the quality of this body of literature as a whole is unimpressive, and is clearly unable to determine whether ECT is more, or less, effective than SECT in reducing depression». Additionally, the authors contest that «ECT must be assessed using the same standards applied to psychiatric medications and other medical interventions, with placebo-controlled studies as the primary method for assessment». In their view, «major flaws have to be ignored to claim that ECT is more effective than SECT. […] we just don't know whether ECT is better than, worse than, or no different from, placebo» (Read, Kirsch and McGrath, 2019).

As outlined above, the practice of ECT is anchored in well-grounded evidence that meets current standards, shared with other full-medical sciences. In Sackeim's words, «the evidence indicating that ECT is effective in the treatment of mood disorders is diverse, long-standing, and incontrovertible» (Sackeim, 2017). Rather than being reported anecdotally, such evidence should be weighed and interpreted in the context of the extensive state-of-the-art literature composed by all levels of evidence, including randomised trials of ECT versus SECT and ECT versus pharmacotherapy; randomised comparisons of different technical parameters in ECT; as well as prospective, representative studies conducted in both the hospital and community settings (Sackeim, 2017).

Psychiatry should be approached as an evolving, evidence-based practice, rather than a sort of cookbook medicine. The authors' claim seems to neglect the fact that ECT is primarily delivered to a population of patients that are either urgently/emergently ill or unable to be rescued by more standard interventions (Abrams, 2002; American Psychiatric Association, 2001; Roose and Sackeim, 2004). In this scenario, which evidence-based principle justifies a randomised comparison of ECT with an inactive control? Or, as Goldberg (2021) asked: «to what nonexperimental, evidence-based therapy does one refer MDD patients who are unresponsive to five or more monoaminergic antidepressants […] – if not ECT?»

While of major scientific importance, the methodology used in randomised controlled trials may not be feasible for the recruitment of complex populations (such as treatment-resistant elderly depressed patients with increased medical and psychiatric comorbidity) or for the assessment of life-saving interventions, in which ECT may surely be included (Heijnen *et al*., 2010; Cattaneo *et al*., 2020; Goldberg, 2021). Likewise, it is an observational approach derived from clinical practice that provides evidence to support the use of electrical defibrillation in cardiac arrhythmias (Cattaneo *et al*., 2020) or the use of penicillin in meningococcal meningitis (Guyatt *et al*., 2008).

The lack of modern, placebo-controlled studies proving that ECT is a life-altering (often, lifesaving) intervention in elderly depressed persons does not preclude its effectiveness in the real clinical setting (consider, for example, the small-to-medium effect sizes of monoaminergic antidepressants compared with placebo, described by Turner *et al*., 2008), nor does it invalidate more than eighty years of extensive research. Rather than active versus sham treatment comparison trials, which presumably will not be replicated again (Rasmussen, 2009), the field of ECT practice and research would be better served by conducting non-inferiority clinical trials comparing ECT with alternative active, higher-potency treatments (Goldberg, 2021).

2.3.3 ECT compared with antidepressant drugs

There is ample non-randomised (Abrams, 2002) and randomised trial evidence (as summarised in Janicak *et al*., 1985; Kho *et al*., 2003; Pagnin *et al*., 2004) showing the unequivocal statistical superiority of ECT over antidepressant pharmacotherapy (including serotonin reuptake inhibitors, tricyclics, and monoamine oxidase inhibitors) in the short-term treatment of MDD. Early studies conducted during the pre-pharmacological era generally reported response rates from 80% to 90% in ECT-treated depressed patients, when used as first-line treatment (Prudic *et al*., 1996).

Correspondingly, recent research has shown that rates of remission to ECT fall in the range of 52% – 90% (Petrides *et al*., 2001; Husain *et al*., 2004a; Sienaert *et al*., 2010; Fink, 2014; Kolshus, Jelovac and McLoughlin, 2017), which largely exceeds the ones documented in sequential medication trials (Whyte *et al*., 2004; Rush *et al*., 2006). In the largest prospective, randomised antidepressant treatment trial to date in outpatients with nonpsychotic MDD, remission rates after each of the first two treatment steps were about 30%. Of clinical concern is the subsequent decline in remission rates as more treatment steps were required (Rush *et al*., 2006).

The superior efficacy of ECT as compared to antidepressant pharmacotherapy, in terms of both quality and speed of response, has also been demonstrated in treatment-resistant (being the study by Folkerts *et al*., 1997 the only that has addressed this issue directly) and elderly depressed patients (Salzman, Wong and Wright, 2002; Greenberg, 2005; Spaans *et al*., 2015). In clinical trials, ECT was often employed as the gold-standard intervention against which to evaluate the efficacy of the first (at that time, newer) antidepressants and, in plain words, no trial has ever found an antidepressant therapy to be more effective than ECT in the treatment of major depression (to put this discussion in proper context, see American Psychiatric Association, 2001 and Roose and Sackeim, 2004). It should be noted, however, that no studies have compared the efficacy of ECT with that of newer antidepressant medications (such as mirtazapine or venlafaxine), even though the comparative efficacy of antidepressants does not differ substantially (Roose and Sackeim, 2004; Royal College of Psychiatrists, 2019).

On the other hand, the lack of randomised trials of ECT versus pharmacological treatment in the elderly poses a lacuna in the evidence. Regardless, in the current state of affairs both the clinical significance and the ethics of such comparisons would be dubious (Roose and Sackeim, 2004; Goldberg, 2021).

2.3.4 ECT in elderly patients

The published literature from the past decades clearly supports the efficacy of ECT in the treatment of elderly patients with MDD (Stek *et al*., 2003; Roose and Sackeim, 2004; Frazer, Christensen and Griffiths, 2005; Heijnen *et al*., 2010; Geduldig and Kellner, 2016; Kellner *et al*., 2016a), even in those referred to as the oldest-old (the lower threshold of which is arbitrarily defined as between ages 75 and 85) (Tomac *et al*., 1997; Tew *et al*., 1999; Manly, Oakley and Bloch, 2000; Burke, Shannon and Beveridge, 2007; Narang *et al*., 2018). As a Cochrane systematic review pointed out, this large body of literature largely consists of non-randomised studies (Stek *et al*., 2003).

Overall, remission rates in the old-age population are impressively high, typically ranging from 73 to 90% (Tew *et al*., 1999; O'Connor *et al*., 2010). Another critical issue regarding the role of ECT in geriatric depression is the speed of symptom reduction. Elderly depressed patients treated with ECT have been shown to achieve response and remission significantly faster in comparison with other age groups (Rhebergen *et al*., 2015) or with those treated with antidepressant medication (Spaans *et al*., 2015). In fact, significant clinical response can be demonstrated after a single session (Williams, O'Brien and Cullum, 1997). The cohort of elderly major depression remitters (n = 133) of the Prolonging Remission in Depressed Elderly (PRIDE) study, who were given a course of ultra-brief right unilateral ECT augmented with venlafaxine, required a mean (standard deviation) of 7 (3.1) acute treatments to complete remission. Of these, almost half remitted within 2 weeks, requiring six or fewer treatments (Kellner *et al*., 2015). Yet, there is no evidence whatsoever from which one could postulate the optimum number of ECT sessions that are required to achieve a therapeutic response (American Psychiatric Association, 2001).

In clinical practice the response trajectories over the ECT course can be variable and fairly unpredictable, implying that ECT should not be discarded when rapid response/remission is not seen

(Williams, O'Brien and Cullum, 1997). A recent retrospective, naturalistic follow-up study (n = 81) reinforces this view, confirming that MDD patients who do not achieve remission after an acute series of 12 ECT sessions still hold a reasonable chance of remission within 6 months (van Duist *et al*., 2020).

This same rapidity of action was replicated in a prospective naturalistic study involving a large sample (n = 402) of elderly patients with TRD (Socci *et al*., 2018), and is of particular note considering that, overall, patients in the ECT group have a higher degree of treatment resistance and a more severe clinical presentation (Spaans *et al*., 2015; Socci *et al*., 2018). Earlier remission may well be an outcome criterion of paramount clinical importance for an elderly person who is severely depressed, as it will be illustrated in Chapters 3 and 4 of this dissertation.

2.3.5 Influence of age on short-term ECT outcome

The influence of age on ECT outcomes has been a subject of interest and research, with conflicting results been yielded. Some studies concluded in favour of a positive association between older age and response to ECT (Tew *et al*., 1999; O'Connor *et al*., 2001). However, in neither of these reports proper adjustment for potential confounders was undertaken (see Birkenhäger *et al*., 2010; Socci *et al*., 2018 for review). By contrast, in recent studies where analysis was adjusted for the length of the index episode and psychotic features, as potential confounding factors, old age had no significant effect on the attainment of response and remission. The effectiveness of an acute course of ECT in older depressed patients is at least equal as compared with younger patients (Birkenhäger *et al*., 2010; Damm *et al*., 2010; Socci *et al*., 2018). Therefore, it can be hypothesized that the putative superior response to ECT among geriatric patients may reflect age-related clinical and symptomatologic factors that determined their referral in the first place (Roose and Sackeim, 2004; Socci *et al*., 2018), including higher prevalence of psychotic and melancholic features in later life (as further detailed in Chapter 3).

This pattern of responsivity is nuanced compared to other physical interventions in the treatment of major depression and merits special consideration. Firstly, old recipients of ECT show a higher burden of somatic comorbidities and greater cognitive impairment at baseline, compared with younger groups. Secondly, a higher rate of treatment resistance has been demonstrated in the elderly. Thirdly, there is indeed an age-related difference in seizure duration, whereby a higher seizure threshold and a decreased seizure duration are consistently associated with rising age. These findings make the effectivity of ECT in the population of elderly patients all the more impressive (Roose and Sackeim, 2004; Birkenhäger *et al*., 2010; Damm *et al*., 2010; Socci *et al*., 2018). Yet, there is an important question still unanswered: how favourable are ECT treatment outcomes among elderly depressed individuals who failed several antidepressant trials?

2.3.6 The use of ECT in TRD in the elderly

The literature has produced diverging findings as to whether a prior history of failed treatment trials negatively influences the efficacy of subsequent ECT. A slew of early studies found treatment resistance to be associated with poor ECT outcome in major depression, with rates of response/remission ranging from approximately 30% to 100% (Prudic *et al*., 1996; Dombrovski *et al*., 2005; Khalid *et al*., 2008). More recently, data from a large multi-centre study (n = 328) found previous medication resistance to be a predictor of nonremission in major depression patients following an acute course of ECT (OR = 1.67, 95% CI = 1.05 to 2.67), with a 50% remission rate among the nonpsychotic, medication-resistant patients (Dombrovski *et al*., 2005). Though systematic data on this is still scarce, a recent meta-analysis of seven observational studies performed by Heijnen *et al*. (2010) concluded that the efficacy of ECT is significantly superior in patients without previous pharmacotherapy failure as compared with medication-resistant patients (overall remission rates of 64.9% and 48.0%, respectively). However, the authors noted that three of the studies did not show, per se, a significant difference

between the two patient groups. They also addressed inherent biases and additional limitations that could have impacted the results, including confounding factors and weaknesses of the treatment protocol (it is likely that the use of right unilateral ECT, for example, underestimated its effectiveness).

These findings are in apparent disagreement with the results of other studies (Pluijms *et al*., 2002; Husain *et al*., 2004a; van den Broek *et al*., 2004; Rasmussen *et al*., 2006; Khalid *et al*., 2008). Data from the STAR*D study has hinted that the challenge of prospectively identifying individuals who will not remit after the first or second treatment steps will not be addressed by clinical or demographic descriptors. For the time being, it seems that only a time-consuming sequence of empirical treatment trials can identify TRD patients (Rush, 2011). Rasmussen *et al*. (2007), from the Consortium for Research in ECT, have shown that antidepressant medication treatment failure does not predict acute remission in nonpsychotic depressed patients treated with ECT (n = 345). In keep with this, a prospective, naturalistic study of the effectiveness of ECT in major depression patients (n = 38) failed to identify any correlation between the number of previous unsuccessful treatments and the magnitude of improvement achieved with ECT. By contrast, these authors found that ECT remains an effective treatment even in patients who failed to respond to an average of 5.4 different pharmacological trials. Indeed, about half of such patients achieved remission and two thirds met response criteria (Khalid *et al*., 2008). More recently, a large prospective trial recruiting TRD patients treated with bilateral ECT (n = 402) reported rates of response and remission in the elderly that amounted to 70% and 30%, respectively (Socci *et al*., 2017).

Varying response rates in patients with previous pharmacotherapy failure are deemed inevitable, depending, among others, on the adopted definition of treatment resistance and on the characteristics of treatment protocol. Nonetheless, these studies make clear that treatment resistance does not close out a favourable response to ECT (American Psychiatric Association, 2001; Royal College of Psychiatrists, 2019). In fact, while patients with treatment-resistant major depression may have lower response and remission rates after an acute course of ECT, compared to their non-resistant counterparts, the general outcome remains substantial and does not seem to diminish further with the more failed trials (Khalid et *al*., 2008; Damm *et al*., 2010). This result is encouraging for such a population, especially when one considers the remission rates of 13%-14% after the third and fourth treatment steps with conventional antidepressants (Rush *et al*., 2006).

2.4 Safety and Tolerability of ECT

While the unsurpassable efficacy of ECT for the treatment of TRD and other psychiatric conditions is well proved, this treatment conjures up fears of severe and sustained adverse effects from patients, caregivers, and healthcare professionals. The fear of adverse effects on cognition, in particular, remains perhaps as the major impediment to its use, both on the part of patients and practitioners (American Psychiatric Association, 2001; Kellner, Obbels and Sienaert, 2020). In this section, the safety and tolerability of ECT are briefly overviewed, on the basis of today's practice.

2.4.1 Medical complications

Surprising to some, ECT is consistently regarded as one of the safest procedures performed under general anaesthesia (American Psychiatric Association, 2001; Nuttall *et al*., 2004; Blumberger *et al*., 2017; Tørring *et al*., 2017). The rate of mortality attributed to modified ECT (performed under general anaesthesia and with muscle relaxation) is extremely low, comparing favourably to that of minor surgery or normal pregnancy. A systematic review with pooled analysis, covering data from 32 developed and developing countries over a period of 40 years, estimated the ECT-related mortality to

be 2 patients per 100,000 treatments (Tørring *et al*., 2017). Cardiovascular complications, related to the major physiological effects of ECT on this organ system, are the main cause of mortality and significant morbidity with ECT, and this is particularly relevant in the elderly (American Psychiatric Association, 2001; Roose and Sackeim, 2004). Notwithstanding, significant cardiovascular events are infrequent and manageable with prophylactic treatment, tending to occur in the immediate postictal period (American Psychiatric Association, 2001). A recent systematic review and meta-analysis showed that major adverse cardiac events (such as myocardial infarction, arrhythmia, and acute heart failure) occur in approximately one out of every 50 patients receiving ECT or, alternatively, in one of every 200 sessions of ECT (Duma *et al*., 2019). The type of preexisting cardiac disease is believed to predict the type of cardiovascular complication that may arise after ECT (Zielinski *et al*., 1993).

As is the case with any treatment requiring general anaesthesia, the risk of medical complications related to ECT is higher in elderly individuals or in those with medical comorbidities, especially cardiac illness. A thoughtful medical evaluation following evidence-based protocols is therefore critical in high-risk patients, with a view to anticipate/prevent possible adverse events and optimise the baseline medical conditions prior to ECT (American Psychiatric Association, 2001). However, it is worthy to emphasize that patients referred for ECT often suffer from severe psychiatric illnesses that may pose a threat to life (examples include catatonia, neuroleptic malignant syndrome, and mood or psychotic disorders with severe suicidal ideation, as it will be illustrated in Chapters 3 and 4). Accordingly, the risk/benefit analysis must consider the risks of not offering or not administering ECT. This is the rational that drove the APA Task Force Report on ECT to state that there are no absolute contraindications for this procedure (American Psychiatric Association, 2001).

2.4.2 Cognitive adverse effects

In simple terms, ECT is associated with four types of adverse effects on cognition that are highly stereotyped: confusional state immediately following ECT; impaired executive function; anterograde amnesia; and retrograde amnesia.

The most marked cognitive adverse effects are observed in the acute period after ECT, being disorientation, impaired attention, and amnesia the most frequent. This clinical picture is self-limited and typically does not exceed a total of 30 minutes (American Psychiatric Association, 2001; Kellner, Obbels and Sienaert, 2020).

Impaired executive function is subacute and resolves by 15 days after completion of the ECT course (Semkovska and McLoughlin, 2010). There is no objective evidence of persisting impairment of cognitive functions following ECT and, should it occur, the contribution of the underlying psychiatric condition is not to be neglected (American Psychiatric Association, 2001; Semkovska and McLoughlin, 2010). On the contrary, ECT has been shown to improve long-term performance with regard to several cognitive and executive functioning measures (Semkovska and McLoughlin, 2010), irrespective of age (Bosboom and Deijen, 2006). A similar improvement has also been replicated in cohorts with treatment-resistant depression (Fujita *et al*., 2006; Bodnar *et al*., 2016; Stojanovic *et al*., 2017).

Anterograde amnesia, referring to the impairment in remembering newly learned information, is common among ECT recipients and is also characterized by a subacute course. It resolves within a period of days to weeks following termination of ECT. This is the justification for recommending initial restrictions on activities such as driving and working. There is virtually no evidence of cumulative cognitive impairment with repeated courses of acute or long-term ECT (American Psychiatric Association, 2001; Semkovska and McLoughlin, 2010).

Retrograde amnesia refers to the impaired ability to remember autobiographic or public information acquired in the past and, not surprisingly, is the most feared ECT-induced cognitive effect. Most patients will have deficits in retrograde amnesia to some degree, but it is not possible to predict

their extent on an individual basis. Memory for events that occurred several months to years prior to commencing ECT is more susceptible to loss than memory from the remote past. As with anterograde amnesia, changes in retrograde amnesia post-ECT are more likely to occur with bilateral electrode placement and increased number of treatments. It is known that patients with baseline neurologic impairment are at increased risk (American Psychiatric Association, 2001; Kellner, Obbels and Sienaert, 2020). Some data indicate that time to reorientation after ECT may be a proxy for the degree of persistent retrograde amnesia following the treatment course (Royal College of Psychiatrists, 2019). Overall, retrograde amnesia reduces significantly within weeks of the end of the ECT course, but persistent or permanent memory loss has been reported (American Psychiatric Association, 2001; Roose and Sackeim, 2004; Kellner and Farber, 2016).

In clinical practice, several factors related to the treatment technique (laterality, stimulus dose, pulse width, amongst others) exert a substantial influence on the nature and magnitude of cognitive deficits and can therefore be used as a means to prevent or attenuate them. The best evidence currently available is clear, in that adverse effects of ECT on cognition are limited and transient, both in the adult (Semkovska and McLoughlin, 2010) and in the geriatric population (Tomac *et al*., 1997; Kumar *et al*., 2016; van Rooij, Riva-Posse and McDonald, 2020). Notably, cognitive performance is expected either to improve or to remain unchanged within the 6-month period following ECT, even though inter-individual variability is considerable (Obbels *et al*., 2018).

To conclude, the adverse effects associated with ECT represent more a concern about tolerability rather than safety of this procedure. In fact, ECT may be even safer than pharmacological treatment, particularly in the vulnerable population of geriatric patients. Kellner and Farber (2016) proposed an analogy to illustrate the magnitude of the benefits and risks of ECT measured against each other:

> Many cancers are lethal, life-threatening illnesses for which treatments (surgery, chemotherapy, and radiation) carry considerable risks. Patients rarely categorically refuse cancer treatments because of concerns about adverse effects, yet this happens frequently with ECT. Our contention is that refusing ECT because of concerns about memory loss is equivalent to refusing cancer chemotherapy because of concerns about hair loss. These effects are unpleasant and upsetting, but not worth risking one's life over. Just as the side-effects of chemotherapy abate, so too do those of ECT; most of the hair grows back, most of the memories return, and the patient's life is saved.

Chapter 3

Use and Practice of ECT at a Secondary Care Hospital in Portugal: a 3-year retrospective chart review

3.1 Material and Methods

The data presented here were drawn from the electronic medical records of patients treated with ECT at Hospital de Vila Franca de Xira (HVFX), a secondary care, general teaching hospital located in Vila Franca de Xira, Portugal. The psychiatric unit of this hospital includes 25 inpatient beds. This study covers a three-year period, from 2018 (the inception of the ECT service at HVFX) to May 2021. The study protocol was reviewed and approved by the local ethics committee.

3.1.1 Study sample

The flowchart for patient selection, including exclusion criteria, is presented in Figure 5. All patients treated with ECT at HVFX were initially considered (n = 27). For any given patient treated with ECT, only the last acute series delivered in the inpatient or outpatient setting was examined (referred as the index ECT course), comprising a total of 97 ECT treatments. This was devised as a methodological approach to handle missing data, as is cases in which the first ECT course was unrecoverable. Patients who prematurely withdrew from the index ECT course prior to the fourth session (n = 6) were operationalised as premature dropouts; reasons for dropping out were collected but these patients were excluded from the descriptive analysis. Those dropping out later were defined as late dropouts (n = 5) and included in the study. One additional patient, deemed non-responsive to the index ECT course, was excluded from this study because the treatment management was regarded as suboptimal: considering her diagnosis of treatment-resistant bipolar I disorder, anticonvulsant medications were maintained during the index ECT course, which is known to interfere with seizure expression (American Psychiatric Association, 2001); secondly, the ECT device, at that time, was not prepared to digitally record the EEG activity during the procedure. Patients with missing data within the medical record (n = 2) were also excluded. Finally, a retrospective analysis of the electronic medical records of all eligible patients (n = 18) was undertaken.

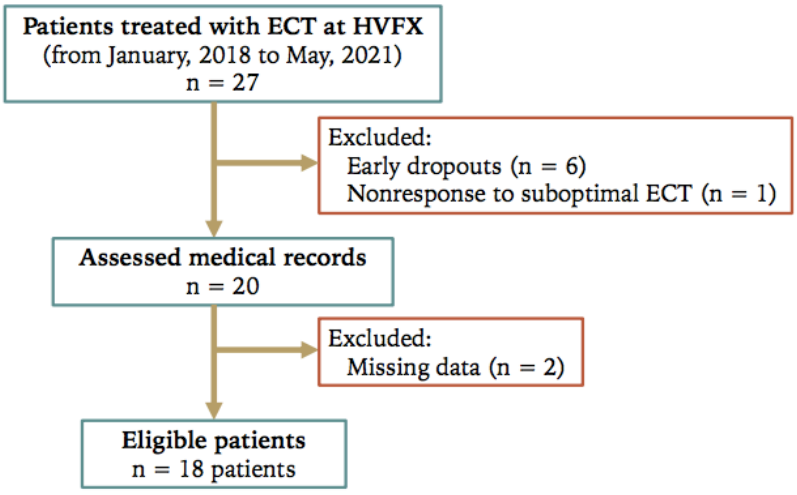


Figure 5. Flowchart of patient selection.

3.1.2 Pre-ECT evaluation

The routine pre-ECT evaluation was performed by the ECT psychiatrist (the supervisor of this dissertation). On a general basis, it included: a complete psychiatric history and examination, including the assessment of past response to ECT and other treatments; a careful medical history and physical examination, with an emphasis on the neurologic, cardiovascular, and pulmonary status; routine laboratory workup (including a complete blood count, the thyroid panel, and an ionogram), an electrocardiogram, and a brain computed tomography scan; if relevant to the case, a note written by the ECT psychiatrist in the patient's clinical record, summarising the indications for and risks of ECT, and proposing any further modification or evaluation required; an anaesthetic assessment; and the patient's written informed consent for ECT (American Psychiatric Association, 2002). All patients were considered to be capable of providing written informed consent for ECT, based on the judgment of the ECT psychiatrist. A written informed consent for anaesthesia was obtained separately. Whenever possible, family members were involved in the consent process.

When possible, patients were withdrawn from benzodiazepines and mood stabilizers the night before ECT, as well as in the morning of the procedure. Other psychotropic medications were allowed during the ECT course, based on the clinical judgment of the treating psychiatrist.

3.1.3 Ratings on prior treatment resistance/nonresponse

A history of treatment resistance/nonresponse was investigated through the inpatient and outpatient medical records. Considering that no universal definition for treatment-resistant unipolar or bipolar depression exists, this study adopted criteria implemented by other authors (Brown *et al*., 2019), in keeping with the clinical experience of the ECT psychiatrist. Thus, resistance or nonresponse to previous pharmacological treatments was defined as follows: in patients with unipolar MDD, insufficient clinical improvement (i.e., failure to achieve remission) from at least 2 adequate trials with pharmacologically different antidepressants; in patients with unipolar MDD with psychotic features, in addition to the preceding criterion, a lack of response to a concomitant antipsychotic medication was required; in bipolar patients (I or II), insufficient clinical improvement from first-line medications (such as lithium or lamotrigine) plus atypical antipsychotic treatment (Fujiwara *et al*., 2016; Brown *et al*., 2019). The level of treatment nonresponse for the index episode of each patient (namely, the number, type, and duration of adequate unsuccessful trials) was not formally assessed. However, almost all patients considered by the treating team to be resistant had failed numerous pharmacological trials.

3.1.4 ECT procedure

All patients were lying in the supine position. Anaesthesia was routinely induced by intravenous etomidate (0.15-0.30 mg/kg), relying both on its favourable properties in eliciting an adequate seizure during ECT and on its stable cardiovascular profile. Propofol (0.75-1.5 mg/kg) and ketamine (2-3 mg/kg) were used as alternative anaesthetic agents. The preferred muscle relaxant was succinylcholine (0.5–1.0 mg/kg), administered as an intravenous bolus. After anaesthetic induction, patients underwent manual bag-mask ventilation with 100% oxygen. Physiological monitoring included vital signs and peripheral oxygen saturation. A disposable bite block was inserted into the patient's mouth before the delivery of the electrical stimulus.

ECT was performed using a Thymatron® System IV device (Somatics Corp, LLC). Stimulus was delivered in the form of constant-current, pulsed square waveform. All patients were initially treated with bifrontal stimulus electrode placement, and brief (0.5 millisecond) or ultra-brief (0.25-0.3 millisecond) pulse widths. Stimulus intensity was established at the first treatment using the empirical dose titration method or, alternatively, the half-age method, as described in detail by the APA Task Force on ECT (American Psychiatric Association, 2001). Motor and electroencephalographic (EEG)

seizure activity were monitored, and the ECT practitioner privileged the latter over the former. Therefore, the cuff technique, applied for timing of convulsive movements, was omitted. The therapeutic seizure endpoint was defined as the elicitation of an EEG seizure of at least 20 seconds' duration, as measured by the electroencephalogram. In the case of subconvulsive stimuli (EEG seizure activity < 20 seconds) and/or too low postictal suppression index (PSI < 80%), subsequent restimulations were conducted at 50%-100% above the original stimulus dosage (1.5-2.5 times the seizure threshold). A maximal number of 4 trials were performed during each session, with an interval of approximately 20 seconds between restimulations. In case of prolonged convulsive activity (here defined as longer than 2 minutes by motor or EEG criteria), the seizure was aborted using an anaesthetic agent with anticonvulsant properties (e.g., propofol).

During the treatment course, stimulus dosage was adjusted upward to maintain a consistent suprathreshold level. If potential adverse effects on cognitive functioning posed a challenge, patients were crossed over to unilateral (versus bifrontal) stimulation of the non-dominant (typically right) hemisphere. The number of ECT treatments to be administered in the index course was determined by the prescribing practitioner on the basis of clinical observation, as per international guidelines (American Psychiatric Association, 2001). ECT was continued until the patient was asymptomatic (i.e., in remission), had reached a plateau in response, or when intolerable side effects occurred. Acute ECT was usually administered in the inpatient setting, and the average treatment series comprised 6 to 10 sessions on a twice-a-week schedule, when possible. Once the treatment technique was optimised, a minimum of 10 sessions was required before deeming a patient to be an ECT nonresponder (American Psychiatric Association, 2001).

Technical and electrophysiological parameters of the ECT procedure were digitally recorded at each treatment session, and a hard copy output of the EEG activity was retained. Adverse effects of ECT were systematically documented in free form.

3.1.5 Evaluation of treatment outcome

Clinical evaluation of psychiatric symptoms was conducted by the treating psychiatrist between each ECT treatment, on a daily, as-needed basis. Patients' clinical assessment was generally predicated on subjective and objective indicators of treatment outcome (response/remission), here gathered through the review of each procedure note. Occasionally, psychopathological rating scales such as the Young Mania Rating Scale (YMRS) and the sign-based measure of psychomotor disturbance (CORE) were applied.

Response was defined as partial and sustained improvement in the patient's psychiatric status. Full symptomatic remission, the primary outcome measure, is defined as the absence of psychiatric symptoms that is sustained on subsequent measurements. The secondary outcome criterion is the time between the index ECT session and the response or remission. In the present study, early symptom change was regarded as significant improvement in patient symptoms reported to occur within 4 or less ECT sessions.

3.1.6 Continuation and maintenance ECT

Some patients were prescribed continuation ECT (c-ECT), given for up to six months after treatment of the acute index episode, and/or maintenance ECT (m-ECT), administered beyond those six months, with the aim to prevent relapse and recurrence, respectively. The choice, frequency and duration of c-ECT and m-ECT varied on a case-by-case basis and were also recorded.

3.1.7 Data extraction

The study's variables were operationalised according with well-suited approaches adopted by relevant studies (Husain *et al*., 2004b; Perugi *et al*., 2017). Data were extracted from the hospital records using an electronic abstraction form designed for the purpose of this study and approved by the ECT psychiatrist. This research database was built on the Protection Policy applied by HVFX (available at https://www.hospitalvilafrancadexira.pt/politica-de-privacidade-geral#), in compliance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on Personal Data Protection.

Data were collected on sociodemographic (sex, age at index episode, occupation, marital status) and illness-related variables (age at onset, primary psychiatric diagnosis, psychiatry comorbidity, number of prior psychiatric hospitalisations, reason for admission, length of the index episode, length of the index hospitalisation). The burden of medical morbidity was assessed retrospectively by organ system using the Cumulative Illness Rating Scale (CIRS) for the younger group and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) for the elderly, following the guidelines published by Miller and Towers (1991). The scoring sheet was completed individually, whenever possible, using information available up to the date of the index episode.

Data related to the index ECT course were also collected (indication criteria, history of previous ECT, number of treatment sessions, treatment outcomes, adverse effects, rates of relapse and recurrence whenever applicable, continuation/maintenance ECT), including technical and electrophysiological parameters (electrode placement, motor and EEG seizure activity, PSI). The inpatient ECT prevalence rate (iP%) was calculated as the proportion in percent of ECT-treated patients out of all patients admitted to the psychiatric ward (the inpatient population). For this estimate, access to an administrative database was provided.

Data were extracted from the records by one rater (the author of the study), who was familiarised with the hospital's health information system. This investigator coded the data independently, under the supervision of the ECT psychiatrist. Further issues arising during the coding process were discussed in periodical meetings with the ECT psychiatrist.

Finally, the author conducted an informal face-to-face interview to the ECT psychiatrist to determine local barriers limiting access to ECT.

3.1.8 Data analyses

Clinical variables and ECT-related data were compared between young (18-59 years) and geriatric (≥ 60 years) patients. In keeping with the small size of the study population, power analysis calculations were not performed. Instead, standard descriptive analyses were presented in terms of mean, median, range, and standard deviation (for continuous variables) or frequency distributions (for categorical variables). For some variables (number of ECT sessions required for response/remission), 10^{th} and 90^{th} percentiles were also presented. Rates of response and remission were indicated in percentages (%) and frequency (n). The percentage of patients with reported adverse effects related to the index ECT course was calculated. Rates of relapse/recurrence were also displayed.

3.2 Results

3.2.1 Sociodemographic characteristics

Both sexes were evenly represented. Eight patients (44.4%) were aged 60 years and older (Figure 5), henceforth referred as the old group or the elderly.

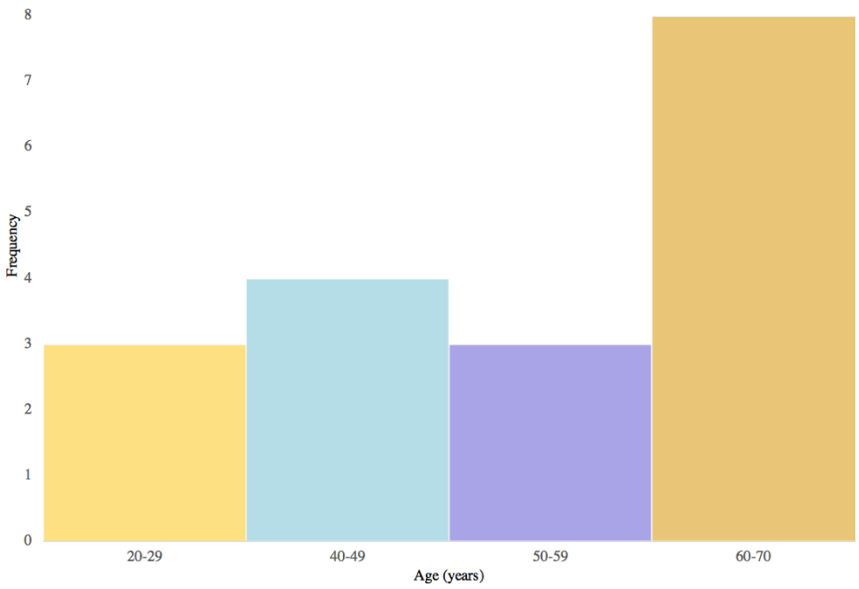


Figure 6. Age distribution in the total sample (absolute frequency).

Table 1 gives the sociodemographic and clinical features of the study sample (n = 18), and separately for the two age groups. The average age at index episode was 39.5 years in the younger-old patients and 62.7 years in the old group. The mean age at onset of the primary psychiatric illness ranged from 31.8 years among the younger patients to 45.2 years in the old ones. More than a quarter of the patient sample (29.4%) had at least three prior hospitalisations (range: 0 to 12).

The mean length of the index episode was 12.0 and 8.2 weeks in younger and old patients, respectively. Approximately 67% of the patient sample was diagnosed with a lifetime comorbidity. Among the younger subjects (n = 7; 70%), the following groups were represented: maladaptive personality traits, cannabinoid use, postpartum depression, alcohol use disorder, obsessive-compulsive disorder, and somatic symptom disorder; among the elderly, 5 patients (62.5%) had a positive history of intellectual disability, anxiety disorder, alcohol use disorder, iatrogenic parkinsonism, and/or delusional jealousy.

Table 1. Sociodemographic and clinical features for the total sample, and separately for the two age groups of ECT-treated patients.

Variable	**18-59 years (n = 10)**	**≥ 60 years (n = 8)**	**Total sample (n = 18)**
Female, n (%)	4 (40)	5 (62.5)	9 (50)
Employment status, n (%)			
Employed	2 (20)	0	2 (11.1)
Unemployed	4 (40)	0	4 (22.2)
Sick leave	2 (20)	1 (12.5)	3 (16.7)
Retired	2 (20)	7 (87.5)	9 (50.0)
Marital status, n (%)			
Single	3 (30)	0	3 (16.7)

Married/cohabiting	5 (50)	6 (75)	11 (61.1)
Divorced	2 (20)	1 (12.5)	3 (16.7)
No information provided	0	1 (12.5)	1 (5.5)
Age at index episode, mean (SD), y	39.5	62.7	49.8 (15.5)
Range	20-57	60-69	20-69
Age of onset, mean, y	31.8	45.2	37.8 (16.2)
Range	15-54	25-68	15-68
No. of previous psychiatric hospitalisations, mean	1.9	3.4 [a]	2.5
Range	0-10	0-12	0-12
n (%)			
0	3 (30)	2 (28.6)	5 (29.4)
1	3 (30)	1 (14.3)	4 (23.5)
2	3 (30)	1 (14.3)	4 (23.5)
≥ 3	1 (10)	4 (57.1)	5 (29.4)
Length of index episode, mean (SD), weeks	12.0 [b]	8.2	10.1 (55.7)
Range	1-24	0.4-20	0.4-24
Psychiatric comorbidity, n (%)	7 (70)	5 (62.5)	12 (66.7)
CIRS/CIRS-G total score (SD)			
Mean	9.9 [c]	13.1 [a]	10.0 (4.1)
Median	11.5	12 [a]	12
Range	5-11	9-20	5-20

Abbreviations: CIRS, Cumulative Illness Rating Scale; CIRS-G, Cumulative Illness Scale-Geriatric version; ST, standard deviation.
[a] n = 7 (score not available for 1 subject)
[b] n = 5 due to missing values
[c] n = 8 (score not available for 2 subjects)

3.2.2 Medical comorbidity

At baseline, a slightly higher CIRS-G total score was documented in old patients compared to the mean CIRS score found in younger ones (13.1 and 9.9, respectively). The main medical comorbidity in our sample was cardiac abnormalities (n = 11; 61.1%), and preexisting cardiac conditions were especially prevalent among the elderly (n = 6; 75%).

3.2.3 Diagnosis at index episode

Table 2 provides the primary psychiatric diagnosis at the index episode by sex and age group, according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). The most common primary diagnoses fit into the ICD-10-CM category of mood disorders, representing 83.3% (n = 15) of all sampled patients. This predominance was observed in both sexes (66.7% in male and 100% in female patients), as in both age groups (80.0% in younger subjects and 87.5% in old ones). Considering the whole sample, the codes F31.x [bipolar disorder] were the most frequent (n = 9; 50.0%), of which the codes F31.30-F31.5 [bipolar disorder, current episode depressed] were the most represented (n = 4; 22.2%). This group was followed by the codes F33.x [major depressive disorder, recurrent] (n = 4; 16.7%). All patients diagnosed with a severe major depressive

episode (single or recurrent) with psychotic features belonged to the old age group, accounting for 37.5% of this population.

The second most frequent primary diagnosis was schizophrenic disorders (n = 3; 16.7%). In this specific group, the most common diagnosis was F29 [unspecified psychosis] (n = 2; 11.1%), followed by catatonic schizophrenia (n = 1; 5.6%). All the individuals with a schizophrenic disorder as the primary diagnosis were male patients.

Table 2. ICD-10-CM primary diagnosis of the total sample, by sex, and by age group.

ICD-10-CM codes		Sex		Age	
	n (%)	Male, n ($\%_{\text{within sex}}$)	Female, n ($\%_{\text{within sex}}$)	Younger, n ($\%_{\text{within age}}$)	Old, n ($\%_{\text{within age}}$)
F20-F29 | Schizophrenic disorders	3 (16.7)	3 (33.3)	0	2 (20.0)	1 (12.5)
F29 Unspecified psychosis	2 (11.1)	2 (22.2)	0	2 (20.0)	0
F20.2 Catatonic schizophrenia	1 (5.6)	1 (11.1)	0	0	1 (12.5)
F30-F39 | Mood disorders	15 (83.3)	6 (66.7)	9 (100)	8 (80.0)	7 (87.5)
F31 – Bipolar disorder	9 (50)	2 (22.2)	7 (77.8)	5 (50)	4 (50)
Bipolar I mania	2 (11.1)	0	2 (22.2)	1 (10.0)	1 (12.5)
F31.2 Current episode manic severe with psychotic features	2 (11.1)	0	2 (22.2)	1 (10.0)	1 (12.5)
Bipolar I depression	4 (22.2)	1 (11.1)	3 (33.3)	2 (20.0)	2 (25.0)
F31.30 Current episode depressed, mild or moderate severity	2 (11.1)	1 (11.1)	1 (11.1)	1 (10.0)	1 (12.5)
F31.4 Current episode depressed, severe, without psychotic features	1 (5.6)	0	1 (11.1)	0	1 (12.5)
F31.5 Current episode depressed, severe, with psychotic features	1 (5.6)	0	1 (11.1)	1 (10.0)	0
Mixed episode	1 (5.6)	1 (11.1)	0	1 (10.0)	0
F31.63 Current episode mixed, severe, without psychotic features	1 (5.6)	1 (11.1)	0	1 (10.0)	0
Other bipolar disorders	2 (11.1)	0	2 (22.2)	1 (10.0)	1 (12.5)
F31.81 Bipolar II disorder	1 (5.6)	0	1 (11.1)	1 (10.0)	0
F31.9 Unspecified	1 (5.6)	0	1 (11.1)	0	1 (12.5)

Major depressive disorder		6 (33.3)	4 (44.4)	2 (22.2)	3 (20.0)	3 (37.5)
F32 – Single episode		2 (11.1)	2 (22.2)	0	1 (10.0)	1 (12.5)
F32.1 Moderate		1 (5.6)	1 (11.1)	0	1 (10.0)	0
F32.3 Severe with psychotic features		1 (5.6)	1 (11.1)	0	0	1 (12.5)
F33 – Recurrent		4 (16.7)	2 (22.2)	2 (22.2)	2 (10.0)	2 (25.0)
F33.2 Severe without psychotic features		1 (11.1)	1 (11.1)	0	1 (10.0)	0
F33.3 Severe with psychotic symptoms		2 (11.1)	1 (11.1)	1 (11.1)	0	2 (25.0)
F33.41 In partial remission		1 (5.6)	0	1 (11.1)	1 (10.0)	0
	Total	18 (100)	9 (50.0)	9 (50.0)	10 (55.6)	8 (44.4)

3.2.4 Indication for and details of the index ECT course

Table 3 summarises the main indication criteria and characteristics of the index treatment course. A small fraction had a previous history of ECT (n = 5; 27.8%). The most common indication for ECT was prior unsuccessful pharmacological treatments (n = 9; 50.0%). This was followed by catatonia/neuroleptic syndrome (n = 2; 11.8%), previous good response (n = 2; 11.8%), and patient's preference (n = 2; 11.8%). Other indications included drug intolerance (n = 1; 5.9%), persistent food refusal (n = 1; 5.9%), severe suicidality (n = 1; 5.9%), and delirious mania (n = 1; 5.9%).

Table 3. Indication criteria and characteristics of the index ECT course.

Variable	**18-59 years (n = 10)**	**≥ 60 years (n = 8)**	**Total sample (n = 18)**
History of previous ECT, n (%)	2 (20)	3 (37.5)	5 (27.8)
Main indication criterion			
Low responsivity to medication	4 (40)	5 (62.5)	9 (50)
Catatonia/neuroleptic malign syndrome	2 (22.2)	0	2 (11.8)
Drug intolerance	0	1	1 (5.9)
Food refusal	0	1 (12.5)	1 (5.9)
Severe suicidality	1 (11.1)	0	1 (5.9)
Delirious mania	1 (11.1)	0	1 (5.9)
Previous good response	1 (11.1)	1 (12.5)	2 (11.8)
Patient's preference	1 (11.1)	1 (12.5)	2 (11.8)
No. of acute ECT sessions, mean	4.8	5.4	5.1
Range	1-13	3-10	1-13
EEG seizure activity (1st session), mean, sec	54.1	23.8 [a]	41.6
EEG seizure activity, mean, sec	32.9 [b]	30.7	31.8
PSI, mean (%)	53.7 [b]	46.4 [c]	50.6
Length of index hospitalisation, mean, days	31 [d]	72.2	56.4
Median	20	72	55
Range	6-64	11-145	6-145
Time ECT – hospital discharge, mean, days	12.75 [e]	35.1	27.7

Abbreviations: SD, standard deviation; EEG, electroencephalographic; PSI, postictal suppression index.

[a] n = 7 due to missing values

[b] n = 8 due to missing values

[c] n = 6

[d] n = 5

[e] n = 4

The mean number of acute treatments for the total sample was 5.1, the median was 4.0, and the 10th and 90th percentiles were 1 and 10. Younger patients received a mean number of ECT sessions virtually similar to that of the old group (4.8 and 5.4, respectively). Results concerning the duration of motor and electroencephalographic (EEG) seizure activity are presented as a boxplot in Figure 6.

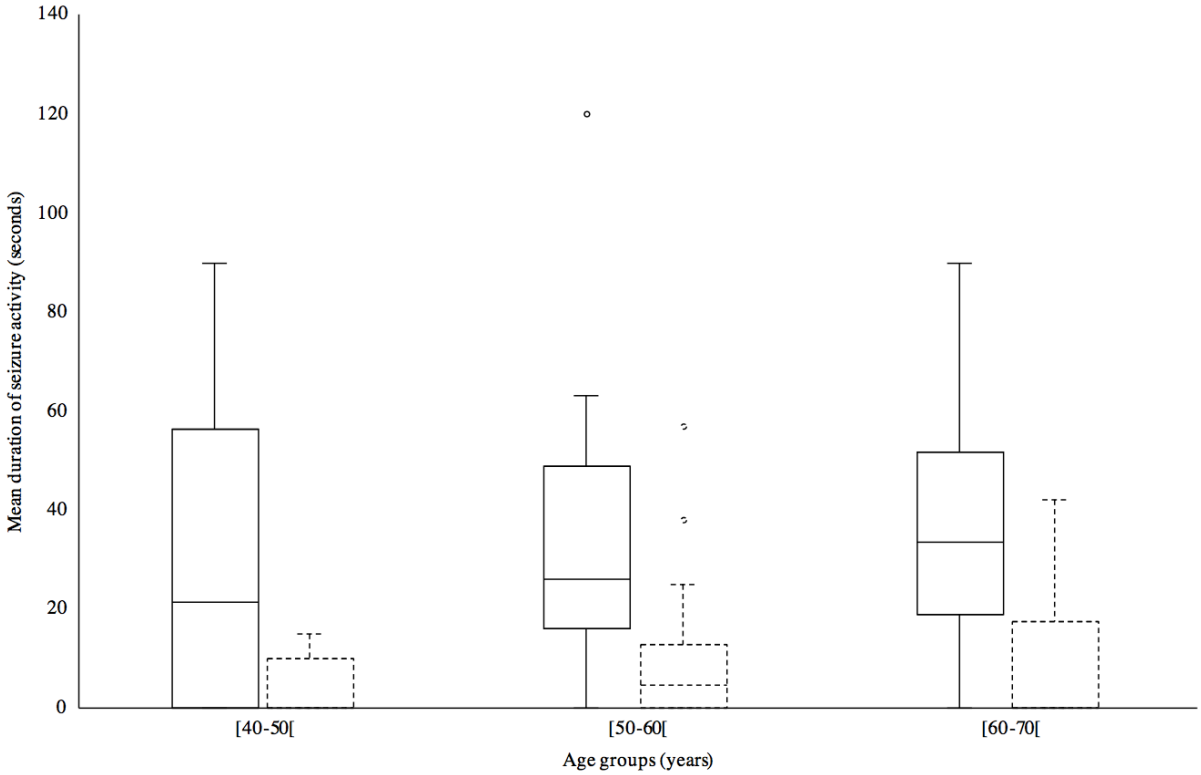


Figure 7. Boxplots regarding the mean duration of motor and electroencephalographic seizure activity by age, for each patient. The solid and dashed lines represent electroencephalographic and motor seizure activity, respectively. Within each box and whisker plot: the median is marked by horizontal lines; boxes span the interquartile range of each group's distribution of values, between the lower and upper quartiles; the whiskers extend to the highest and lowest observations that are located within 1.5 times the interquartile range; dots denote outliers.

For those whose index ECT course was delivered in the inpatient setting (n = 14), the median length of stay was approximately 31 days for the younger patients and 72 days for the old ones (interquartile range, 16 to 77 days). The mean time elapsed between the first ECT session and hospital discharge was approximately 13 days among the younger patients and 35 days in the old group, with an interquartile range of 5 to 19 days for the whole sample.

The inpatient ECT prevalence rate (iP%) for the study period was 1.9%. The iP% calculated for the pre-pandemic period (from 2018 to February 2020) was 2.5%. The iP% on the first year of activity of the ECT unit at HVFX (from 2018 to 2019) was 4.0%.

3.2.5 Treatment outcomes

Altogether, 88.2% (n = 15) of the sample achieved an early symptom change by the fourth ECT session, a group in which all the younger and 75% (n = 6) of the old patients were included. Of this group of early responders, 12 (80%) eventually attained remission.

At the end of the ECT course, 13 (72.2%) patients met the criteria for remission (Figure 7). Among the younger age group, 40% (n = 4) were classified as responders and 60% (n = 6) as remitters; in the old group, one patient was classified as nonresponder and 87.5% (n = 7) attained remission.

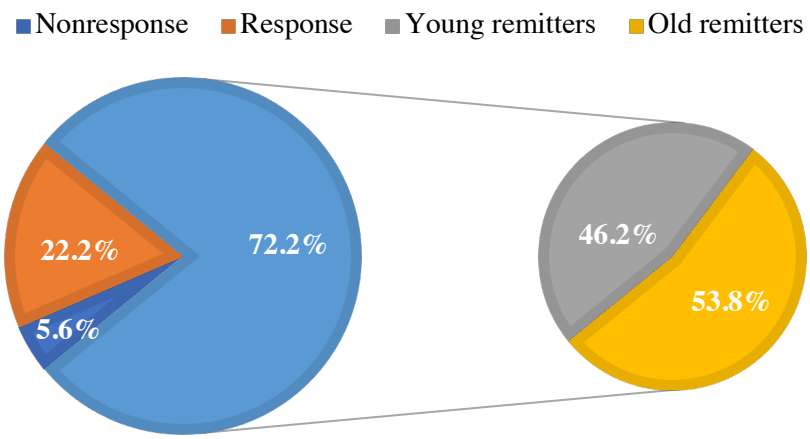


Figure 8. Proportion of patients classified as nonresponders, responders and remitters after completion of the index course of ECT.

The group of remitters received a mean of 4.4 and a median of 4 ECT sessions (10th and 90th percentiles: 1 and 9). The mean number of ECT sessions needed to achieve full remission was virtually similar in both age groups (4.2 in the younger group and 4.0 in the old group). For the total sample, 33.3% (6/18) were declared remitters after having received, at most, 3 ECT sessions. Half of the patient sample attained remission at or before the fifth ECT session. The increase in the number of remitters with a rising number of ECT treatments was almost linear, as shown in Figure 8.

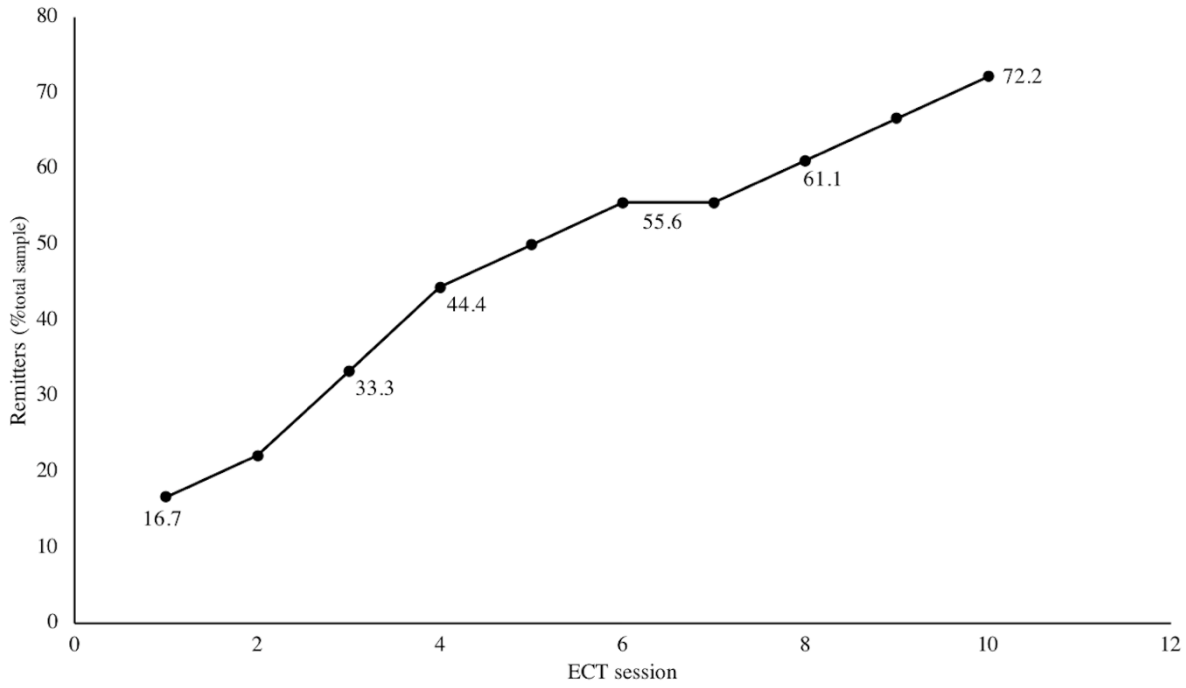


Figure 9. Cumulative percent of sampled patients achieving remission by ECT session (n = 13/18).

3.2.6 Treatment-related adverse effects

Data about ECT-related adverse effects are summarised in Table 4. Self-limited and mild adverse effects associated with ECT occurred in approximately 60% of the total sample. No life-threatening or major events were reported in any of the patients. The most common adverse effects were heart rate changes (transient tachycardia/bradycardia or increased blood pressure) immediately after the procedure (n = 6; 33.3%), followed by prolonged seizures (n = 4; 22.2%), urinary incontinence (n = 4; 22.2%), motor agitation (n = 2; 11.1%), retrograde amnesia (n = 1; 5.6%), myalgias (n = 1; 5.5%), and oxygen desaturation during recovery from ECT (n = 1; 5.6%). The patient experiencing subjective memory complaints during the index ECT course was switched to right unilateral ECT. When examined by age, the most frequent adverse effects in younger and elderly patients were post-ECT heart rate changes (n = 4; 40%) and urinary incontinence (n = 3; 37.5%), respectively.

Table 4. Reported adverse effects for the index ECT course.

	18-59 years (n = 10)	**≥ 60 years (n = 8)**	**Total sample (n = 18)**
Post-ECT heart rate changes, n (%)	4 (40)	2 (25)	6 (33.3)
Prolonged seizures, n (%)	2 (20)	2 (25)	4 (22.2)
Urinary incontinence, n (%)	1 (10)	3 (37.5)	4 (22.2)
Motor agitation, n (%)	1 (10)	1 (12.5)	2 (11.1)
Retrograde amnesia, n (%)	0	1 (12.5)	1 (5.6)
Post-ECT myalgias, n (%)	1 (10)	0	1 (5.6)
Post-ECT oxygen desaturation, n (%)	1 (10)	0	1 (5.6)

3.2.7 Dropouts

Of all patients treated with ECT at HVFX, 22% (6/27) were regarded as early dropouts. Reasons for dropping out are displayed in Table 5.

Among the eligible patients included in the descriptive analyses, 27.8% (5/18) were classified as late dropouts. The primary reasons for treatment discontinuation were treatment-related adverse effects (n = 3), including post-ECT bradycardia and myalgia; poor adherence to psychiatric treatments (n = 1); or constraints related to the coronavirus 2019 pandemic (n = 1).

Table 5. Reasons for premature dropout (< 4 consecutive ECT treatments) among all patients treated with ECT at HVFX.

	18-59 years (n = 2)	**≥ 60 years (n = 4)**	**Total sample (n = 6)**
Post-ECT confusional state, n (%)	0	1 (25)	1 (16.7)
Poor family support, n (%)	0	2 (50)	2 (33.3)
Not willing to follow, n (%)	2 (100)	1 (25)	3 (50)

3.2.8 Continuation/Maintenance ECT

Of the total sample, 50% of patients underwent continuation ECT and 31.2% maintenance ECT. At follow-up, 25% (2/8) of the younger subjects and 37.5% (n = 3) of the elderly patients had an episode of relapse or recurrence. The treatment outcomes in the short and long term, for the total sample and the two age groups, are summarised in Table 6.

Table 6. Treatment outcomes for the total sample and across the two age groups.

	18-59 years (n = 10)	**≥ 60 years (n = 8)**	**Total sample (n = 18)**
Early symptom change, n (%)	9 (100) [a]	6 (75)	15 (88.2)
Remitters, n (%)	6 (66.7) [a]	7 (87.5)	13 (72.2)
No. of sessions needed to remission, mean	4.2 [b]	4	4.4
Continuation ECT	3 (37.5) [c]	5 (62.5)	8 (50)
Maintenance ECT	2 (25) [c]	3 (37.5)	5 (31.25)
Relapse/recurrence, n (%)	2 (25) [c]	3 (37.5)	5 (31.25
Late dropouts (≥ 4 ECT consecutive ECT sessions)	3 (37.5) [c]	2 (25)	5 (31.25)

[a] n = 9 due to missing values
[b] n = 6 due to missing values
[c] n = 8

3.2.9 Barriers to access

A face-to-face interview conducted with the ECT coordinator at HVFX (my supervisor) is instructive of the many other stumbling blocks that emerge in the path once ECT is offered to and accepted by the patient, even in a hospital where ECT is available. Of these nongeographical barriers, three were highlighted: 1) inadequate availability of qualified professional staff, with a particular emphasis being given to the lack of anaesthesiologists; 2) lack of a specific treatment area (ECT is performed in the general operating room, and thus the number of treatments are dependent of the operating schedule; and 3) attitudinal barriers expressed by the patients and health care professionals, as a disinclination for or a manifest opposition to ECT.

3.3 Discussion

3.3.1 The overall picture

Although a growing body of evidence supports the use of ECT as a gold-standard treatment for a number of psychiatric conditions, in clinical practice this intervention does not stand up likewise. To date, there is a scarcity of updated data concerning the contemporary use of ECT in Portugal (Sienaert and van den Broek, 2009; Mota *et al*., 2021), a country that has thereby been overlooked in international studies on ECT (Ottosson and Fink, 2004; Leiknes, Schweder and Høie, 2012; Lesage *et al*., 2016). In

parallel, there are no national guidelines for its use. Against this backdrop, the present study may have important implications.

Treatment with ECT was implemented in HVFX in 2018, five years after its opening, following an audit conducted by the Joint Commission International (JCI). Despite the small sample size of this study, which makes it underpowered, it provides evidence of ECT treatment patterns and outcomes in a real-world practice setting, with an emphasis on a population that is otherwise unrepresented in clinical trials: the severely ill elderly patients who have severe medical or neuropsychiatric comorbidities. I am not aware of other published studies conducted in Portugal evaluating these parameters on ECT-treated patients, to which the present results could be compared. Given the inherent limitations of this study, the results should be considered preliminary, and the conclusions should be interpreted with caution (see "Strengths and limitations" section).

Beginning with the sociodemographic profile, the patient sample had extraordinarily low levels of employment at baseline, with almost 90% being unemployed, on sick leave, or retired. These results reflect the burden of mental disorders at the individual and societal levels, experienced by all age groups (Whiteford *et al*., 2013).

The mean age at index episode was 49.8 years, which falls within the average range of 49 to 66 years described for ECT-treated European patients (Leiknes, Schweder and Høie, 2012). When analysed by age, this sample is comparable to the inpatient population evaluated by Mota *et al*. (2021) in the national setting, who found a mean age of 50.5 years from 2008 to 2015. Although in our country the frequency of psychiatric disorders is known to be higher in women (Caldas de Almeida *et al*., 2013), including among psychiatric inpatients (Mota *et al*., 2021), we did not observe a predominance of woman over man, as is the trend in other ECT studies conducted in Western European countries (Birkenhäger *et al*., 2010; Damm *et al*., 2010; Perugi *et al*., 2016; Socci *et al*., 2018).

In today's practice, major depression (either unipolar or bipolar) has been regarded as the most common diagnostic indication for ECT in Western countries, especially after a long road of iterative antidepressant trials (Roose and Sackeim, 2004; Kellner, Obbels and Sienaert, 2020). In alignment with this, the present sample was mostly characterised by severally ill patients with mood disorders. Bipolar disorder was the most frequent diagnosis (at the expense of bipolar depression), followed by severe major depression with psychotic or melancholic features (in descending order of frequency). These results are once again consistent with those previously reported by Mota *et al*. (2021), who found that, grossly, 28% and 32% of all ECT-treated inpatients in Portugal have a diagnosis of major depressive disorder or bipolar disorder, respectively. The same authors draw the profile of the typical ECT inpatient in Portugal, described as being a woman above middle age with depressive disorder (Mota *et al*., 2021). As noted above, this is a trend that matches previous data from Western countries (Leiknes, Schweder and Høie, 2012).

Despite its small size, the population of this study illustrates well the panoply of clinical indications for which ECT may be indicated as a first-line (primary) treatment, namely: emergent medical conditions, such as catatonia (including schizophrenia with catatonia and catatonia secondary to critical medical conditions) and neuroleptic malignant syndrome; urgently ill patients who require a rapid treatment response, including those with high suicidal risk, physical deterioration, and/or food and fluid refusal; psychotic mania; and major depression that is poorly responsive to medication or that presents with psychotic/melancholic features. Other candidates in whom the first-line use of ECT should be considered include patients with a prior positive response to this treatment modality, especially in the context of medication resistance or intolerance, and patients who prefer ECT (American Psychiatric Association, 2001). Even though the latter scenario is infrequent, this happens to be the case for at least two of the patients in this study. One of them, in particular, was (at the time of index admission) a 65-year-old woman who attempted suicide by drug overdose. During her

hospitalisation, she proposed to the attending psychiatrist undergoing ECT, since she had had a favourable response to this treatment in a previous episode.

Given the foregoing criteria, and contrary to what is commonly believed, the elderly (including the old-old) constitute a subpopulation that is likely to derive particular benefit from ECT, even (mainly) the patients with a high burden of medical comorbidity. This is because geriatric patients are acknowledged to have increased sensitivity to, and often do not tolerate, the adverse effects of psychotropic medications, which should warrant early reliance on ECT (American Psychiatric Association, 2001; Roose and Sackeim, 2004; Kerner and Prudic, 2014).

In this study, old-age patients had a shorter duration of index episode compared to younger patients, which possibly relates to age-related characteristics that prompted an earlier referral for ECT. Also, this metric is of value considering the well-documented association between protracted duration of untreated illness, worst clinical outcomes (Drancourt *et al*., 2013; Ghio *et al*., 2014), and diminished response rates to all treatments, including ECT (Perugi *et al*., 2012).

3.3.2 ECT effectiveness and speed of response

Among the factors that must be balanced to establish the validity of a medical intervention, efficacy is perhaps the single most important (Ottosson and Fink, 2004). The practice of ECT at HVFX demonstrates that this is an effective treatment for the large majority of its recipients.

Patients in this study followed three distinct trajectory patterns of symptom improvement concerning the index treatment phase: response, complete remission, and nonresponse. On the whole, all but one patient attained response or remission. The largest part of the sample achieved an early symptom change by the fourth ECT session, and the vast majority of this group eventually attained remission. The overall remission rate found in the present study (77.2%) is remarkable and consistent with findings from several studies in mixed-age populations (O'Connor *et al*., 2001; Petrides *et al*., 2001; Husain *et al*., 2004b; Khalid *et al*., 2008; Kellner *et al*., 2010).

Our findings also confirm the superiority of ECT in terms of both the speed of response and remission, an outcome criterion that is of importance per se (Spaans *et al*., 2015). Remission occurred in half of the sample after completion of up to five ECT sessions, which compares favourably with the results published by other authors (Husain *et al*., 2004b; Spaans *et al*., 2015). It is noteworthy that around 17% of all patients were classified as remitters after a single ECT session. The cumulative increase in the percentage of remitters was lower for subsequent sessions within the index course but steady, thereby suggesting the substantial impact of the first treatment in a series. This result builds on previous studies specifically addressing the time course of response to ECT, and a few of them warrant mention.

Rodger, Scott and Whalley (1994), treating 11 major depressive patients that were not receiving concurrent pharmacological treatment with bilateral ECT, reported a 6-fold difference in Hamilton Rating Scale for Depression (HAM-D) scores over the first three sessions as compared to the remainder. In a sample of 47 major depressive patients treated with bilateral ECT, Segman *et al*. (1995) noted a substantial effect of the first ECT session, which contributed to a mean (SD) decrease of 24% (30%) of the total change that occurred in HAMD-D-21 score over the entire treatment. More recently, a multisite, collaborative study from the Consortium for Research in ECT, sponsored by the National Institute of Mental Health (NIMH), gave more strength to these earlier results. In the first phase of the study, patients with unipolar major depression, scoring a minimum of 21 in HAM-D at baseline, received an acute course of bilateral ECT (n = 131). The decrease in suicidal intent, as measured by item 3 of the HAM-D, was higher after the first session (Kellner *et al*., 2005). Looking at the whole cohort (n = 507), the percentage decline in HAM-D scores was highest after the first ECT session in the treatment series, decreasing by an average of 25% from baseline (Kellner and Knapp, 2007).

Additionally, in the largest randomised controlled trial to date comparing the efficacy of the three electrode placements in ECT, Kellner *et al*. (2010) found a reduction of 48% in HAM-D-24 total scores only after the first treatment in series.

Taken together, these studies point out that the first session(s) of ECT may exert a disproportionate role concerning treatment outcome. The hypothesis raised by Kellner and Knapp (2007) to explain this curious result is the well-known phenomenon that seizure threshold increases over the treatment course, thus making it harder to electrically evoke a seizure of therapeutic value. In fact, the elicitation of an adequate seizure is consensually accepted as a sine qua non for the therapeutic benefits of ECT. What is not clear is how best to define seizure adequacy (American Psychiatric Association, 2001). Regardless, seizure length alone does not correlate with the effectiveness of ECT and is unlikely to be a good parameter of seizure quality (American Psychiatric Association, 2001; Royal College of Psychiatrists, 2019). In a large, retrospective review of ECT patients (n = 519), Rasimas, Stevens and Rasmussen (2007) found that the major decline in seizure length was observed from the first to the second treatments and thereafter remained constant for all age groups, up to the end of the series. Other indices of seizure adequacy, including postictal suppression and global (particularly delta) EEG power, have emerged as promising, qualitative criteria to routinely monitor seizure adequacy in ECT practice (Royal College of Psychiatrists, 2019). This point will be further discussed with regard to the third clinical case presented.

After the completion of the index treatment, ECT was tapered off whenever possible and appropriate. Rescue ECT was implemented on an as-needed basis when the recrudescence of symptoms became apparent. Further continuation ECT was instituted in half of the patients of this sample. This practice has been proved to decrease the likelihood of relapse (as reviewed by Kellner, Obbels and Sienaert, 2020) over the 6-month period after an acute ECT course, which is known to be substantial and more accentuated in the first few months (American Psychiatric Association, 2001). Up to 60% of patients relapse even when continuation treatment is provided in the form of aggressive pharmacotherapy (van Rooij, Riva-Posse and McDonald, 2020). It is therefore recommended to offer continuation ECT to most patients after a successful ECT treatment, particularly to those with a history of severe episodes not effectively managed with medication (American Psychiatric Association, 2001; Kellner, Obbels and Sienaert, 2020). It should be noted that the elderly population is not left out from these recommendations. Indeed, the second phase of the recent PRIDE study confirmed the efficacy of as few as four ECT continuation treatments in maintaining the long-term benefits of ECT in the vulnerable population of geriatric patients, following remission (Kellner *et al*., 2016b).

In this study, a minority (25%) of patients relapsed within the first 6 months following the initial treatment with ECT. The length of follow-up (calculated from the first outpatient visit to the date of the present study) was highly variable, ranging from a few months to more than two years. A higher rate of relapse/recurrence would be expected with longer follow-up. No solid conclusions can be formulated about the long-term course trajectories due to the small sample size and the differences in follow-up time between patients.

When the sample of this study is broken down by age, there are additional considerations worth discussing, as far as the elderly are concerned. Around 88% of all geriatric patients (over half of the group of remitters) achieved remission, requiring a mean of 4 ECT treatments to reach this status. These data is very encouraging, not only in comparison with outcomes from the sole pharmacotherapy (Rush *et al*., 2006; Spaans *et al*., 2015), but especially when taking into account that at least half of the total sample had been trialled on extensive medication trials and thus deemed ‘treatment resistant’ before being referred for ECT. Regrettably, the prior treatment history could not be stringently ascertained, and treatment resistance was not assessed by physician-rated instruments (such as the Antidepressant Treatment History Form).

The available evidence supports these findings. Old age acts as a predictor of better response to ECT (Rhebergen *et al*., 2015; Kellner, Obbels and Sienaert, 2020). In line with this, the study published by Spaans *et al*. (2015) provided welcome insights into speed of remission following treatment with ECT versus antidepressant medication, comparing elderly inpatients with severe depression from two previously published randomised controlled trials. The results were clear, if unsurprising: ECT results in substantially faster remission rates in comparison with antidepressants. The pivotal, NIMH-funded PRIDE (Prolonging Remission in Depressed Elderly) study lends further support to the rapidity of action as well to the effectiveness of ECT in the treatment of severe depression in elderly patients. Approximately 62% of all patients were considered remitters after undergoing an acute course of right unilateral, ultra-brief ECT augmented with venlafaxine, requiring a mean number of 7 sessions (over two and a half weeks) to attain remission. The remission rate was reported to be approximately twice the rate obtained with antidepressant medications in similar populations. Notably, about one fifth of the patients needed four or fewer sessions to remission. On the other hand, and similarly to the aforementioned studies, the trajectory of mean HAM-D-24 scores assessed at each treatment revealed a highest decrease after the first ECT procedure, for the total sample and the group of remitters (Kellner *et al*., 2016a).

In sum, ECT has proven to be a rapidly acting and highly effective treatment, particularly for geriatric patients with a severe psychiatric condition. The ethical principle of beneficence compels its use.

3.3.3 Safety and tolerability of ECT

Data from the present study support modified ECT as a safe and well-tolerated treatment across age, when performed in accordance with modern protocols validated by international guidelines (American Psychiatric Association, 2001). All ECT-related adverse effects reported in this patient sample were minor and short-lived. The elderly group, despite a higher documented burden of physical comorbidity at baseline (reflected in higher CIRS-G total scores), appeared to tolerate ECT at least as well as the younger, healthier subjects. Even elderly patients with pre-existing cardiac illness, comorbid cerebrovascular or neurodegenerative disorders who did not tolerate treatment as usual were safely treated with ECT, after international clinical recommendations have been safeguarded (American Psychiatric Association, 2001). Retrograde amnesia, the cognitive effect that raises the most concern among patients, family members, and health care professionals, was reported in only one (elderly) patient during the index ECT course and resolved within 6 months post-ECT. It is of further note that this patient had a known deficit in attention and executive functioning prior to receiving ECT, which was attributed to the underlying psychiatric illness. On the other side of the coin, ECT was continued in the long term with the patient's consent to attenuate parkinsonian and extrapyramidal symptoms caused by lithium and neuroleptics, while maintaining efficacy for bipolar depression.

Of note, these results are susceptible to methodological biases that have a bearing on the frequency of reported adverse events, which most likely underestimate the true incidence (further discussed in the "Strengths and limitations" section). Nevertheless, these data are concordant with the best available evidence from large epidemiological studies (Nuttall *et al*., 2004), systematic and/or meta-analytical reviews (Tørring *et al*., 2017; Duma *et al*., 2019), all acknowledging ECT as a low-risk and well-tolerated medical procedure for the vast majority of individuals. Irrespective of age, the safety of ECT has been demonstrated for patients who suffer from a wide range of medical comorbidities, including neurologic, cardiac, and pulmonary disease (Kellner, Obbels and Sienaert, 2020; van Rooij, Riva-Posse and McDonald, 2020). The cognitive adverse effects associated with ECT may instil a greater concern when it comes to geriatric patients. However, as with clinical effectiveness, negative cognitive effects can, too, be modulated by an appropriate adjustment of technical parameters,

particularly of the electrode placement, stimulus intensity, and electrical waveform. For instance, ultrabrief, unilateral ECT has been proved to minimise the extent of cognitive adverse effects following a course of ECT without hindering its efficacy (American Psychiatric Association, 2001; Kellner *et al*., 2016a).

Like any other medical procedure, the use of ECT poses possible medical risks and adverse effects, the very reason for which the expected treatment-related benefits must be balanced against potential risks on an individual patient basis (American Psychiatry Association, 2001). An example of this is to be seen in the third case report presented in Chapter 4. However, current evidence is unequivocal in noting that potential adverse effects are mild and transient for the vast majority of patients treated with ECT. Thereby, they should definitely not hinder practitioners from prescribing this treatment, nor people in need from considering it (Fink, 2005; Kellner, Obbels and Sienaert, 2020).

In the face of the principle of *primum non nocere* (not doing harm), the tremendous detrimental impact of failing to treat severely ill individuals must not be overlooked. The beneficial effects of modified ECT substantially outweigh the risks in appropriately selected patients. It is not an overstatement to affirm that, in those with a severe psychiatric condition and high morbidity, this intervention is indeed the safest treatment option that could be offered. Therefore, ECT fulfils the ethical principle of non-maleficence, and considerations about the safety and tolerability of this treatment should not limit its use a priori.

3.3.4 Availability of ECT

The overall inpatient ECT prevalence rate for the study period is more than double the value reported by Mota *et al*. (2021) in their pioneering, nationwide study of ECT use, but lag behind the results from other European countries (Leiknes, Schweder and Høie, 2012). However, the question remains whether this figure mirrors an adequate and fair provision of ECT within the municipality of Vila Franca de Xira.

From the review by Leiknes, Schweder and Høie (2012), limited to ECT studies published between 1990 and 2010, the inpatient prevalence rate found in the present study is comparable to the lowest figures found in Australia and in the Nordic countries. Nevertheless, caution must be exerted when comparing results from different studies in this field, and a few fundamental limitations deserve mentioning. First, there is a pervasive lack of official central data across most countries (Sienaert and van den Broek, 2009; Leiknes, Schweder and Høie, 2012; Lesage *et al*., 2016). Consequently, in some cases, less than a handful of studies of questionable representativeness are the only evidence available from which to infer the patterns of ECT use in a given nation. Second, publications differ in the methods of calculating and reporting the outcome variables, expressing ECT use rates in terms of treated person rate, ECT administration rate, inpatient prevalence rate, and/or average ECT number per patient (in a course). This methodological heterogeneity is likely to account for a non-negligible part of the widespread variation that has been reported between estimated rates of ECT use, even within a single hospital, and recommends caution in generalising or comparing such data between and within countries (Ottosson and Fink, 2004; Leiknes, Schweder and Høie, 2012; Lesage *et al*., 2016; Mota *et al*., 2021).

Considering these limitations, the results should be contextualised. Data from the Portuguese Mental Health Study (1st report) revealed that Portugal has the highest prevalence of mental disorders in mainland Europe. Notwithstanding, one third of Portuguese adults with severe mental disorders do not receive psychiatric care (Caldas de Almeida *et al*., 2013). Under this scenario, the finding that just 1.5% of the inpatient psychiatric population of HVFX received ECT over the three-year study period seems to point clearly toward the underuse of ECT to treat severe psychiatric conditions. This is the more remarkable when one considers that HVFX is located in an urban area, where ECT services are far more prevalent (Manique, 2019). This municipality covers over 5% of the population living in

Lisbon city and surrounding counties (the metropolitan area of Lisbon) (Pordata, 2019). Put otherwise, fewer than 6 patients per year are treated with ECT at HVFX, which corroborates the notion that ECT remains notably rare as a medical treatment (Roose and Sackeim, 2004; Lesage *et al*., 2016).

Although our finding lacks generalisability, the same conclusion was evidenced on a large scale by a preliminary nationwide survey (Manique, 2019). This report found no ECT services in almost half (8/18) of the districts of continental Portugal, and the study lacked data from 5 of the remaining. One could hypothesize the existence of a few main centres with ECT facilities to which the patients in need could be referred or transferred. With that being the case, it remains easy to imagine the logistical difficulties posed, for instance, to the patients in pursuit of outpatient or continuation/maintenance ECT. Regardless, at least 11% of all Portuguese hospitals discard ECT as a possible treatment, either because of the geographical distance from an ECT centre or simply because this intervention was not considered at all (Manique, 2019).

These data raise a conflict between the principles of beneficence (doing good) and justice (equality of opportunity for care). As Ottosson and Fink (2004) argued, the «limited access to adequate health care in the world's developed countries for such elemental agents as antibiotics, HIV medicines, vaccinations, and perinatal care is outrageous, but equally so is the denial and unavailability of treatments for psychiatric illnesses». In the light of current standards defining good medical practice, it is hardly thinkable that essential treatments would not be timely delivered to those with an acute myocardial infarction or an acute surgical illness in a developed society. However, this accurately describes the current state of affairs for patients in need of ECT (Ottosson and Fink, 2004).

These restrictions on ECT availability are in conflict with the Resolution for the Protection of Persons with Mental Illness and the Improvement of Mental Health Care (United Nations General Assembly, 1991). To illustrates this point, two of the principles will be transcribed here:

> *Principle 8 – Standards of care*
>
> «Every patient shall have the right to receive such health and social care as is appropriate to his or her health needs.»

> *Principle 14 – Resources for mental health facilities*
>
> «A mental health facility shall have access to the same level of resources as any other health establishment, and in particular: […] (b) Diagnostic and therapeutic equipment for the patient.»

These considerations bring to the fore a discussion about the possible reasons behind the suboptimal use of ECT. The geographic constraints are but one of the determinants of access to ECT services in Portugal, a commonplace shared by many other countries across the globe when ECT is on the table. To complete the picture, ECT training is not a mandatory component of residency training in Portugal, which helps to perpetuate the paucity of psychiatrists privileged to perform this intervention. This is in spite of evidence to suggest that ECT training programs infused with clinical experience lead to more favourable attitudes toward ECT (Oldewening *et al*., 2007). As it stands, I ask: who, if not psychiatrists, will attempt to demystify the social stigma viscerally bound to ECT in the lay community, including in patients, their relatives, and caregivers?

It is thought-provoking that ECT may be denied or not adequately addressed to a patient on the part of psychiatrists who do not feel comfortable treating a severe psychiatric condition by safely delivering an electrical stimulus for therapeutic purposes. This very same problem was incisively articulated by Ottosson and Fink (2004): «Is the primary aim of health care to alleviate suffering in the patients or to make individual health care professionals feel more comfortable?» Complementary, the

same authors asked: «Should the principle of beneficence be sacrificed for the sake of personal ideology?»

These observations are consistent with overall responses collected in the national survey. From the group of hospitals that do not provide ECT, the lack of material resources and/or trained personnel stands as the main reason precluding the availability and use of this intervention (Manique, 2019). On the basis of current standards for the provision of human health care, these do not appear to be valid justifications for withholding critically ill patients from receiving the appropriate treatment. The failure to provide ECT when it is a needed medical treatment does not comply with the ethical principle of justice.

3.4 Strengths and Limitations

This retrospective chart review serves as an example of a real-world approach in an actual clinical practice setting. The importance of such studies has been legitimated as a means of informing regulatory decision-making by authorities such as the European Medicines Agency (Rosso *et al*., 2017) and the US Food and Drug Administration (FDA, 2018). The latter defines real-world data as «data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources» (FDA, 2018). Given the absence of a standardised database structure pertaining to ECT-treated patients at HVFX, data were collected retrospectively from electronic health records. This methodology, considered the most feasible to address the research questions at hand, was chosen for two reasons. First, it provides an economical and time-efficient manner of assessing the ECT effectiveness and safety in usual care practice, and compares ECT treatment patterns adopted at HVFX with international guidelines' standards. The retrospective design of the study controls for the Hawthorne effect on the psychiatrists' performance, a phenomenon whereby a positive bias could have been introduced as a consequence of their awareness of being studied. Secondly, the evidence thus produced can provide valuable insight pertaining to elderly patients with multiple comorbidities, a population often excluded from randomised controlled trials.

As with other types of study, however, there are several inherent weaknesses associated with retrospective chart reviews that need to be carefully addressed. A major limitation lies in the fact that, because information from medical charts was recorded prior to the initiation of the research, a study of this kind is constrained by the historical data retrievable. Some medical records were incomplete or lost in the course of time, deleted by a hacker's attack, raising the issue of having to deal with missing or poor-quality data. This was the primary reason for defining the index ECT course as the last acute course delivered in any given patient. This criterion, in turn, may have introduced a selection bias in the study by increasing the proportion of patients with a history of past ECT. Indeed, previous good response to ECT is a useful predictor of ECT outcome (American Psychiatric Association, 2001) and will tilt the practitioner's decision toward prescribing ECT in subsequent illness episodes. Nevertheless, this subgroup of patients with previous ECT exposure did not achieve a higher remission rate.

The small sample size at our disposal hampers the power of statistical analysis and further limits the generalisability of the data, being the reason why the results are purely descriptive. The COVID-19 pandemic concurred to this constraint, but only to some extent, by imposing reductions in the delivery of acute and continuation/maintenance ECT treatments (Lapid *et al*., 2020; Robertson *et al*., 2021). However, it should be noted that the iP% was 2.5% in the pre-pandemic period.

With respect to data abstraction, there was only one rater in charge of coding the data (the study's author), who was not blind to the purpose of the investigation. This constraint may have introduced a reviewer bias that is not possible to rule out. Preferably, two raters should have been recruited for data

collection and a measurement of interrater reliability presented. In an attempt to partially control for the accuracy and consistency of the data collected, a few patient records were reviewed jointly with the ECT psychiatrist, and periodical meetings were scheduled to clarify any issues that occurred during the coding process.

Another important shortcoming relates to the difficulties in measuring the outcomes of interest. Treatment outcomes were registered by different practitioners, representing an important source of heterogeneity, and not systematically assessed through psychopathological rating scales, thus compromising the validity of the reported outcomes. For a large part of the study population, ECT outcomes were assessed and recorded by the ECT psychiatrist following each ECT session, based exclusively on clinical judgment. Furthermore, a detailed description of the patient's clinical status after each session of ECT was not always available, and, as a consequence, the number of ECT sessions required for response/remission occasionally had to be inferred from subsequent records. A thorough reading of all ECT-related records for the index episode of each patient was conducted in an effort to minimise the impact of these methodological flaws.

There is an additional caveat of particular relevance in regard to a possible measurement bias. Treatment outcomes cannot be framed in a monocausal explanation and contributors other than ECT must be considered, such as the natural history of disease, the placebo effect, and ongoing pharmacological treatment. Under this premise, a limitation worthy of mention is that concomitant psychiatric medications were continued during the index ECT course (except for benzodiazepines and mood stabilisers), and it is known that selected medications increase synergistically the efficacy of ECT (Sackeim *et al*., 2009). While these confounding variables were obviously at play and cannot be excluded in a retrospective study, the sample mainly consisted of patients with a severe psychiatric condition (acute psychotic episode, acute mania, catatonia, severe psychotic or melancholic depression, to name a few). At least half of them had been exposed to several medication trials that did not generate an adequate therapeutic response. Hence, an arguable assumption would be that the influence of a placebo response or other response bias in reported outcomes is not significant.

Another study limitation regards the risk of missed events in reporting the adverse effects associated with ECT. It is possible that milder adverse effects (such as headache, transient agitation, or muscle soreness) were not reported into the clinical files and that subtle cognitive deficits (such as transient amnesia) would have been detected had cognitive scales been routinely used. On the other hand, given that the rate of major events and/or mortality attributable to ECT is extremely low, the relatively small size of the study population skews the results of the analysis.

Finally, the barriers identified to ECT provision at HVFX are uniquely based on the experience and opinion of the ECT psychiatrist, surveyed by personal interview, and do not necessarily reflect the official position or policies of the HVFX.

There is fertile ground in Portugal for real-world research on ECT. Future studies should be carried out to replicate and expand the present findings, considering the challenges here explored.

3.5 Future directions

By no means comprehensive and exhaustive, the present work attempted to capture the current level of performance of ECT delivery in the routine clinical practice of a Portuguese mental health service. This gives us a descriptive picture that is acknowledged to be a key component of any situational analysis aimed at creating a new agenda for change and, in response, at enhancing the provision of health care (World Health Organisation, 2006). As such, I believe that it is of major importance to address some of its implications from a clinical standpoint and to foresee priorities for future action.

There are several opportunities for shortening the knowledge and treatment gaps in medical care involving ECT. At the present time, we lack official, patient-level repositories regarding ECT provision, which would allow benchmarking against professional standards. Such real-world data could be pooled and compared by regional and national bodies to provide a robust baseline understanding of the current patterns in ECT use and practice throughout the country. A shared registry system for ECT across all ECT units (public and private) has been proposed and successfully implemented as a strategy to improve documentation standards (Banken, 2003; Leiknes, Schweder and Høie, 2012; Lesage *et al*., 2016; Scottish ECT Accreditation Network, 2019). Equally important would be to systematically explore, in all institutions providing psychiatric care, the local barriers (whether they are geographical, economic, professional, cultural, or sociopolitical) that may be limiting the prescription and/or use of ECT.

Accessibility and equity are two dimensions of healthcare quality highly dependent on how mental health services are organised (World Health Organization, 2006). The low and uneven rates of ECT use in Portugal raises a pressing issue for mental health care policies targeted at addressing the unmet needs of the underserved regions of the country. Likewise, the development of national or regional guidelines on ECT practice should be encouraged, so as to streamline its use according to the best standards of care. As has been recognised in other countries, a national policy of regular and ongoing monitoring based on agreed-upon guidelines is a valuable means of improving both patient care and the delivery of care. The Scottish ECT Accreditation Network (SEAN), which evolved from an individual quality assurance audit in 1996 to an established accreditation service, serves as an exemplary case (SEAN, 2019).

Not least, the mental health community and the policy-makers committed to health law legislation should be capable of acknowledging ECT on equal terms with other evidence-based medical treatments. In practice, this would translate into safeguarding the ethical imperative of universal and timely, rather than burdened, access to ECT (Ottosson and Fink, 2004; Mota, 2021). From a purely economic standpoint, politicians, decision-makers and other stakeholders should be informed that it is a cost-effective treatment modality for patients whose needs are best met by ECT, which has an unambiguously impact on lowering health-related and economic burdens.

Narrowing down to the professional barriers to providing ECT, the psychiatrist William H. Reid (2009) argues that the crux of change lies in the practicing psychiatrists:

> I have become convinced that the undeserved social stigma attached to ECT by antipsychiatry opponents and media sensationalists cannot be adequately addressed through public education or debate. Two points appear important as we try to make this and other good treatments available to the patients who need them: First, being certain that psychiatrists understand and work with ECT just as they do with other safe and effective treatments, and, second, relying on psychiatrists do make certain that ECT –

and appropriate patient information and advocacy concerning it – is available to patients when it is indicated.

Therefore, a nationwide survey assessing the knowledge and attitudes of the mental health workforce toward ECT would be much welcome. Along with this, the enactment of more ambitious requirements concerning education and training in ECT for all residents in psychiatry is highly warranted. The Portuguese curriculum of psychiatry residency training only requires the acquisition of "theoretical knowledge" about ECT, and no specific goals were established (ordinance no. 340/2016 of 29 December). It seems unlikely that a treatment modality for which no mandatory training is needed during the crucial years of residency will be embraced differently by the psychiatrists of the future in their clinical practice.

The leverage of the current erratic ECT provision toward a consistently high standard will demand concerted efforts from the mental health system as a whole. In consideration of what is left to accomplish, it is my hope that, rather than posing as a stand-alone study, this work may be a contribution toward placing ECT where it should be, sooner rather than later. Hopefully, as Fink (2005) envisioned, «one can be more optimistic that as the interest in evidence-based medicine increases, the proper role of ECT will be recognized, and the present injustices in usage and distribution of facilities will improve».

Chapter 4

Case reports

4.1 Adding ECT to psychopharmacotherapy reduces the time to clinical response, in treatment-resistant depression with psychotic features and catatonia: a case report

Major depressive disorder with psychotic features (hereafter PMD) is defined by the occurrence of a major depressive episode accompanied by psychotic phenomena (delusions and/or hallucinations), frequently consistent with depressive themes (nihilistic, ruin, guilt) (Gournellis *et al*., 2018). Both the point and lifetime prevalence of PMD in the general adult population are estimated to be around 0.4%, increasing in later life (Jääskeläinen *et al*., 2018).

In the post-kraepelinian era, PMD was incorporated among unipolar depressive disorders, despite well-documented evidence that it should be considered a distinct nosological entity. While in International Classification of Diseases – 10th edition (ICD-10), PMD is classified as a subtype of severe depression, in Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5) it falls into the major depressive disorder category, no longer as a severity indicator (Jääskeläinen *et al*., 2018).

The current state of the art indicates that, in comparison to non-psychotic depression (NPD), PMD has distinct onset age, clinical presentation, prognosis, and treatment response. Psychogeriatric studies have shown that individuals with PMD have a later age of onset than NPD counterparts (Jääskeläinen *et al*., 2018). PMD is associated with more motor disturbances, psychosocial impairment, and more frequent relapses. Furthermore, PMD patients have higher rates of suicidal ideation, suicide attempts, and completed suicide, particularly during an acute episode. Diagnostic stability in PMD is reported to be low, although highly age-related (Gournellis *et al*., 2018; Jääskeläinen *et al*., 2018).

Regarding treatment, the proportion of patients with treatment-resistant depression is higher in PMD than NPD (Wagenmakers *et al*., 2020). The standard of care typically consists of combined pharmacologic therapy with an atypical antipsychotic and an antidepressant. Controversy remains about the role of ECT in the current treatment algorithms. Even though its effectiveness and safety have been proved, this method is widely regarded as the last resort after failed pharmacotherapy trials, largely because of its unclear underlying mechanisms of action, safety/ethical concerns, and misrepresentations portrayed in the media not representative of the current practice (Veltman *et al*., 2019; Li *et al*., 2020).

4.1.1 Case Presentation

The inpatient is a 63-year-old man with past medical history of deep vein thrombosis and psychiatric history of alcohol use disorder in the previous five years, with frequent periods of alcohol intoxication. He had family history of depression (his mother committed suicide aged 62 years) and dementia (a paternal uncle, diagnosed at age 68).

In 2019, the patient was brought to a Psychiatry appointment and was admitted in our psychiatric ward with the diagnosis of psychotic depression. He reported feeling depressed, anhedonic and hopeless. Insomnia and weight loss due to decreased appetite were also documented. Upon evaluation, the patient exhibited expressionless gaze, depressed mood without suicide ideation, monosyllabic and provoked speech, increased reaction time, and observable chewing movements. He denied adverse life events. Also of note was the occurrence of prominent delusions of ruin (he believed his family was

financially ruined), reference (he believed that his psychiatrist was communicating directly with him from the TV), and internet-themed delusions (he believed that everything he did was being broadcast over the internet). He was put on first-line treatment with antidepressant and antipsychotics (venlafaxine: 150 mg, q. i. d.; olanzapine: 10 mg, b. i. d.; quetiapine: 100 mg, q. i. d.).

On hospital day 7, psychomotor symptoms (immobility, mutism, rigidity, posturing) were noted. Lorazepam was started to target catatonia, and our patient responded robustly within one hour. His family stated that similar episodes happened at home, occasionally followed by periods of agitation, disorientation, and disorganized behaviour.

On hospital day 11, the patient´s depressive and psychotic symptoms significantly improved. His wife wanted him to be discharged, but the medical staff agreed that careful monitoring was required and deferred the discharge.

On hospital day 17, during a psychotic episode, the patient attempted suicide by cutting both cubital fossae with a razor blade. The nursing and surgical care were provided promptly. Throughout that day and the following one, he displayed indifference towards his act, stating that «the surgeon just sewed outside, the veins remained open».

In the next days, the patient showed fluctuating retarded catatonic symptoms alternating with periods of exuberant delusional activity. At this point we diagnosed him with treatment-resistant major depressive disorder with psychotic and catatonic features. The differential diagnosis included, according to the DSM-V criteria: refractory late-onset schizophrenia with catatonia; treatment-resistant schizoaffective disorder depressive type with catatonia.

Since the patient presented with refractory psychotic and catatonic symptoms, potentially life-threatening (high suicidal intent), we decided to introduce ECT after obtaining informed consent from the patient. The patient's family considered ECT to be harmful and misused by psychiatrists, after viewing clips from the film "One Flew Over the Cuckoo's Nest". His relatives claimed that ECT is a "barbaric method that fries neurons" and that the medical team was responsible for the patient's suicide attempt, asking for his discharge. Several family and multidisciplinary treatment team meetings were conducted, prompted by his wife's and sons' concerns. Throughout this time, the patient remained cooperative and compliant with treatment recommendations, believing that he could benefit from treatment, and thus the voluntary psychiatric hospitalisation was continued. On day 29 the patient began a trial of ECT, resulting in a gradual and dramatic improvement of his medical condition. Time to remission of clinical symptoms following the start of ECT treatment is shown on Figure 9.

After the first c-ECT session, the patient decided to temporarily suspend ECT due to the significant clinical improvement. A case timeline showing progression of psychiatric symptoms, from the inpatient stay in our unit to date, is available (Figure 10).

During the outpatient follow-up period of 17 months, at which point this report was prepared, he remained free of any further mood, psychotic, or catatonic episodes, able to live a functional life.

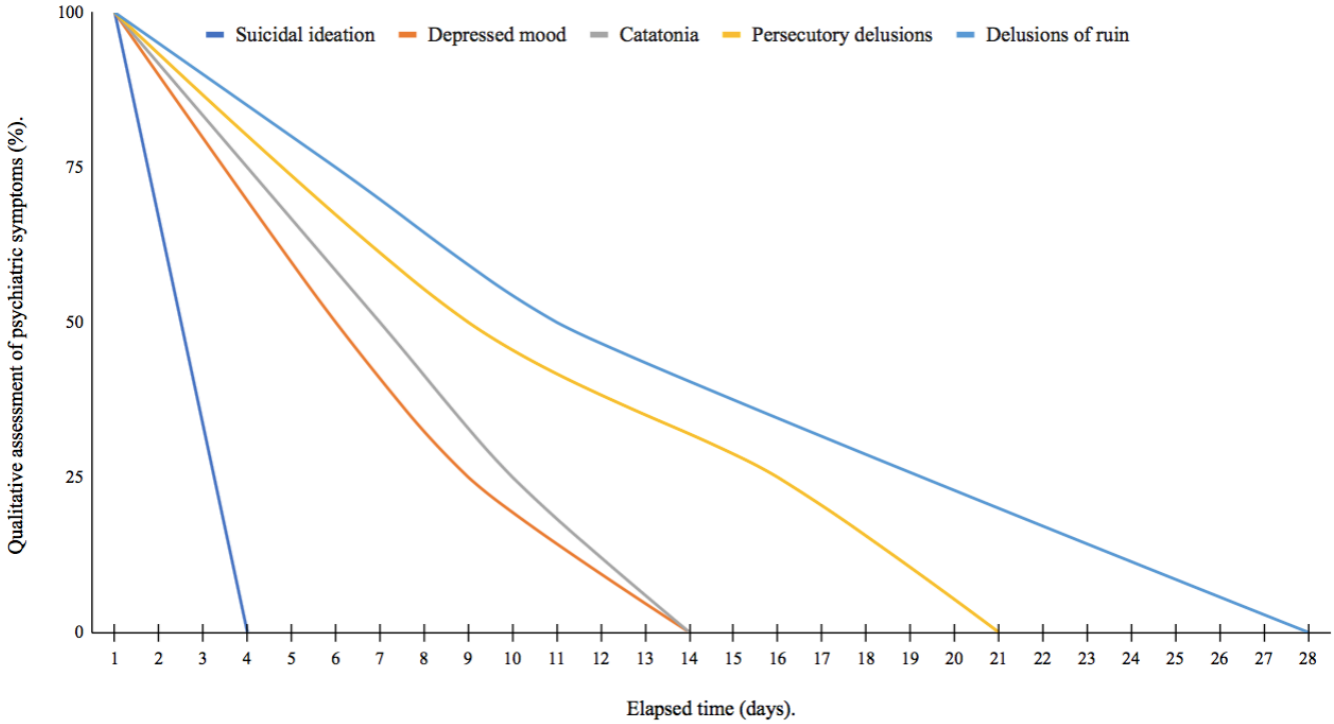


Figure 10. Clinical remission of symptoms throughout inpatient ECT treatment. Each symptom was rated as absent (0 %), mild (25 %), moderate (50%), high (75 %), or severe (100%).

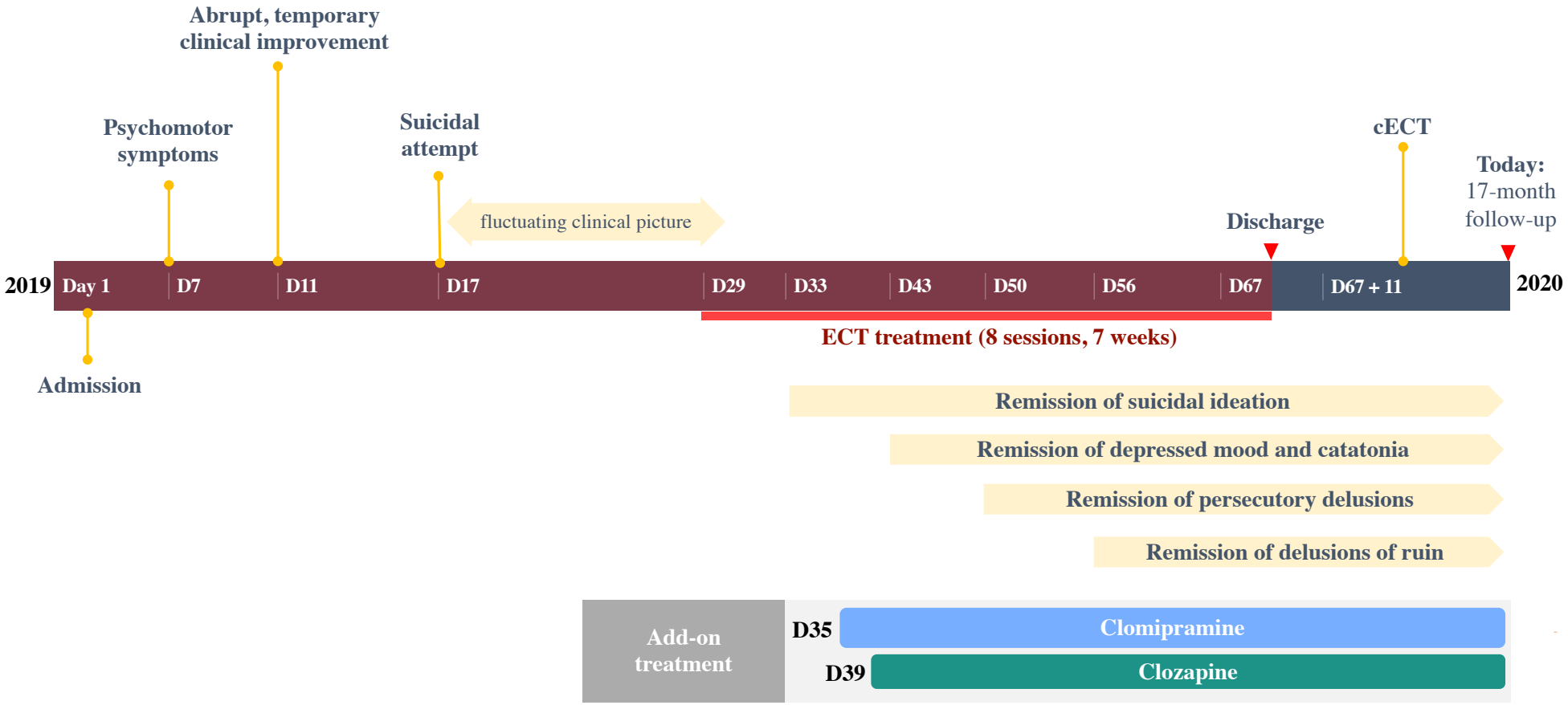


Figure 11. Timeline of progression of the patient's psychiatric status and the treatment regimen during the reported hospitalisation. The reader should note that dates are not spaced out according to a time scale. "c-ECT", continuation ECT.

4.1.2 Discussion

The case presented above highlights a myriad of clinical-ethical issues in the management of a patient with treatment-resistant PMD who is referred for ECT.

First, according to his family, the patient's mental status began to deteriorate in 2017 shortly after stent placement for deep vein thrombosis. While an exhaustive discussion of the crosstalk between thrombosis and psychiatric disorders is beyond the scope of this paper, this is a side issue raised by the presented case. Emerging evidence suggests that the aetiology of venous thromboembolic events may be independently linked to the presence of the mental disorder itself, rather than to antipsychotic medication alone, albeit the underlying biological mechanisms have not yet been fully elucidated (Jönsson *et al*., 2018; Ogłodek *et al*., 2018).

PMD is a disabling and life-threatening psychiatric disorder characterized by the occurrence of episodic psychotic features exclusively within an episode of unipolar depression, a hallmark that differentiates it from other entities, such as bipolar I disorder, schizophrenia, and schizoaffective disorder (Gournellis *et al*., 2018; Jääskeläinen *et al*., 2018). Once a thorough investigation was undertaken and organicity was excluded, the longitudinal course of our patient's illness allowed such diagnosis to be made.

Notwithstanding a large body of literature favouring the conceptualization of PMD as a distinct clinical entity, on par with NPD, PMD is classified as a subtype of depression in both current international diagnostic systems (Jääskeläinen *et al*., 2018). Demographically, the prevalence of PMD is higher in the elderly, particularly in inpatient settings. With respect to symptom profile, the differences extend beyond psychosis: individuals with PMD are more severely depressed, more psychomotorically retarded, and have an increased risk of completed suicide (Gournellis *et al*., 2018; Jääskeläinen *et al*., 2018). Of note, our patient attempted suicide in the context of an acute psychotic event, despite no previously reported suicidal thoughts.

Regarding treatment, the optimal regimen for PMD patients remains nonconsensual. Most guidelines recommend either the antidepressant/antipsychotic combination or ECT for the acute treatment of PMD. Yet, there are no decision trees to establish a rationale for the treatment algorithm.

ECT delivery in PMD, by comparison with NPD, results in earlier symptomatic improvement and significant remission rates. Furthermore, it is the most effective and rapid treatment available for elderly patients with PMD (Veltman *et al*., 2019). Despite its unparalleled effectiveness and safety, modified ECT is nonetheless regarded as a last resort option in clinical practice, as illustrated by the present case, which may perversely prolong the course of illness and increase the likelihood of unfavourable outcomes (Li *et al*., 2020). Sadly, our patient only improved two years after the illness onset, when he underwent ECT treatment due to the presence of partially responsive psychotic and catatonic symptoms associated with high suicide risk. In this regard, it should be noted that the individual's competence to provide informed consent is not necessarily impaired by psychotic illness (Ottosson and Fink, 2004), and that the patient was capable of giving a voluntary informed consent.

The patient was considered an excellent candidate for ECT, owing to the presence of positive predictors of efficacy well established in the literature, including older age, psychosis, depression severity, and catatonia (Veltman *et al*., 2019; Wagenmakers *et al*., 2020). Over the acute course of ECT, it is notable that in 5 out of 8 sessions no motor nor electroencephalographic seizure activity was documented. Psychiatric symptoms improved gradually and robustly during the acute-phase treatment: suicidal ideation was the first symptom to remit, followed by catatonia and depressed mood, persecutory delusions and, finally, delusions of ruin (Figure 9). Retrospectively, the remission of psychotic symptomatology secondarily to resolution of the major depressive episode fits well with the DSM-5 criteria for PMD. Further, this sequential temporal pattern of symptom remission is in line with the evidence that ECT is an effective treatment for acute and short-term resolution of suicidal ideation and

non-responsive catatonia (Braithwaite, 2019). However, the mechanism(s) of action by which the ECT treatment regimen was successful in this individual patient are not fully explained on the basis of current knowledge.

Concerning the prognosis of PMD, early intervention with ECT shortened depressive-episode duration and avoided undue deterioration of the patient's medical condition, restoring his social functioning. Whilst the case report presented here is consistent with existing literature (predicted good response to ECT), the patient had a better treatment prognosis on the long term.

Altogether, this case highlights that, in severely depressed patients, ECT is an excellent add-on to psychopharmacological treatment. The clinicians should consider this treatment approach on an early stage of some severe mental illnesses, including treatment-resistant depression with psychotic and catatonic features.

4.2 Bottom-up neuroanatomical pattern of symptom remission in melancholic depression after electroconvulsive therapy: a case report and literature review

The concept of melancholia or melancholic depression has changed over time, which explains why it is underdiagnosed. Both current diagnostic systems (ICD-10 and DSM-5) position melancholia as one of several specifiers of depression, favouring the consolidation of the unitarian model. In contrast, the binary view recognizes melancholic depression as a categorical depressive syndrome (Parker and Hadzi-Pavlovic, 1996; Veltman *et al*., 2019), mainly supported by the following evidence: (i) primary genetic and biological (vs psychosocial) determinants; (ii) distinctive clinical phenotype (with psychomotor disturbance as a central feature, assessed by the a sign-based measure of psychomotor disturbance [CORE] measure); and (iii) differential treatment response. With regard to treatment, a more favourable ECT outcome is ascribed to melancholic than to non-melancholic depression, although some recent studies have suggested that there is no significant difference (Veltman *et al*., 2019).

4.2.1 Case presentation

We report the case of a 69-year-old woman who has been retired from her post as a medical assistant for five years. Significant medical history included hypothyroidism and hypercholesterolemia. She had no family history of psychiatric illness and no psychiatric background up until April 2017, when she was admitted to a Geriatric Psychiatry Unit due to major depressive disorder with psychotic features (depressed mood, anhedonia, avolition, insomnia, decreased appetite and unintentional weight loss, nihilism, delusions of ruin, hypochondriac ideas). She reported an insidious onset for the past five months and denied triggering factors, notwithstanding her mother's death, one month prior to admission. She showed partial insight regarding her clinical condition and accepted inpatient treatment. Montreal Cognitive Assessment (MoCA) scored 29/30. She was treated pharmacologically with venlafaxine (225 mg, q.i.d.), mirtazapine (30 mg, q.i.d.), risperidone (2 mg, q.i.d.), and lorazepam (1 mg, b.i.d.). After a two-week hospitalisation she was discharged to outpatient follow-up.

In March 2018, she was voluntarily re-admitted in the same Geriatric Psychiatry Unit due to suicidal ideation concomitant with depressed mood, ruminative thinking, hopelessness, loss of appetite, mnesic deficits (difficulty in recalling old events) and early morning awakening insomnia. No psychotic phenomena or behavioural disturbances were documented. The Mini-Mental State Examination (MMSE) and the clock drawing test did not reveal any deficit (she had studied for 4 years and punctuated 29/30 and 7/10, respectively). She was discharged home two weeks later.

In June 2018, she presented to our unit with disturbances in affect (sadness, avolition, anhedonia, and depressive cognitions of worthlessness, hopelessness and helplessness, with no suicidal ideation); psychomotor disturbance (expressed as retardation); cognitive impairment (difficulty remembering recent events and evoking old events); vegetative symptoms (interrupted sleep, early morning awakening, loss of appetite and weight); and psychosis (nihilistic convictions of ruin). Further, she had cystitis on admission (*Escherichia coli* was isolated in the urine on hospital day 5 and was treated with nitrofurantoin). A summary of patient's physical, laboratory and imaging findings is provided in the online version of this article (see Topic S3 of the Supporting Information at the publisher's website: https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fpsyg.12654&file=psyg12654-sup-0001-Supinfo.pdf).

Based on her symptoms, the patient was admitted in our inpatient department for major depressive disorder with melancholic and psychotic features, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, criteria.

On hospital day 12, the patient started an ECT course as an add-on treatment comprising 10 sessions of bifrontal brief pulse stimulation (Topic S4). Vegetative symptoms normalized shortly after the first ECT session (insomnia and appetite loss on hospital days 13 and 15, respectively). From hospital day 20 (after the second session), motoric manifestations showed a gradual and robust improvement. She had a fluctuating course concerning her mood symptoms, ranging from euthymia (on hospital day 21) to depressed mood. However, she judged her mood as non-varying until hospital day 44. In parallel with this, her psychotic symptoms evolved and appeared much improved on hospital days 27 and 44 (after the third and seventh treatments, respectively) but remained present. By hospital day 57 (45 days after ECT had started), all of her symptoms had fully remitted. A significant improvement in post- treatment CORE measure scores was evident (Topic S2). We summarize the acute ECT treatment, including all stimulus parameters and reported adverse reactions in Topic S5.

On hospital day 77, the patient was discharged home and received sertraline (100 mg, q.i.d.), clomipramine (75 mg, q.i.d.), and olanzapine (20 mg, q.i.d.) as add-on treatment. Continuation ECT was given on an outpatient basis throughout a 6-month post-discharge period (Topic S6). The patient remains symptom-free 7 months after the last session of continuation ECT.

The pattern of symptom amelioration suggests that the vegetative symptoms were the first to resolve (her sleep and appetite improved after the first ECT session) (Fig. 11). Motoric manifestations declined significantly in week 1, and in parallel with this, a gradual amelioration of her autonomy in self-care was observed. After the second and third treatments, she reached euthymia and her delusions were resolved, respectively. Nevertheless, she tended to judge her medical status as non-varying (distorted self-perception; see Topic S7). As the course of treatment progressed, both her mood and psychotic symptoms relapsed. By the eighth treatment, her vegetative, motoric, and mood symptoms had significantly improved, but she was still experiencing psychotic symptoms. After 10 treatments, she entered full remission.

4.2.2 Discussion

This report illustrates a case of treatment-resistant depression with melancholic and psychotic features. Fourteen months after the onset of her symptoms (including two admissions to a Geriatric Inpatient Unit), our patient remained unresponsive to medication (a combination of several antidepressants and an antipsychotic). At admission in our psychiatric inpatient unit, her CORE score was as high as 38 points (see Supporting Content 5 for further details). In the face of pharmacotherapy failure and persistent symptoms, we adopted an approach of concomitant antidepressant medication with ECT sessions, starting at day 12.

Generally, seizure threshold (ST) increases during a course of ECT. Among others, individual characteristics (e.g. age) and bilateral electrode placement generally predict a higher ST. Notably, we observed a considerable decrease in our patient's ST over the course of treatment, with the therapeutic charge rate ranging from 25-35% (acute ECT) to 10-15% (continuation ECT), the lowest charge rate of the device. There is no evidence available as to whether this phenomenon occurs in melancholic depression (see Supporting Content 6 for additional content).

During the acute course of ECT, her symptoms improved according to the following sequence: 1) sleep, 2) appetite, 3) motoric, 4) mood, and 5) psychotic symptoms. Hence, the vegetative symptoms were the first to resolve (her sleep and appetite improved after the 1st ECT session). Motoric manifestations declined significantly in week 1 and, in parallel with this, a gradual amelioration of her autonomy in self-care was observed. After the 2nd and 3rd treatments she reached euthymia and her delusions were resolved, respectively. Nevertheless, she would tendentially judge her medical status as non-varying (*distorted self-perception*, see Supporting Content 7). As the course of treatment progressed, both her mood and psychotic symptoms relapsed. By the 8th treatment, her vegetative, motoric and mood symptoms significantly improved, but she was still experiencing psychotic symptoms. After a total of 10 treatments, she entered full remission.

The symptom improvement sequence resembles a pattern of a bottom-up mechanism within the brain anatomy: 1) brain stem, 2) hypothalamus, 3) basal ganglia, 4) limbic system, and 5) brain cortex (Figure 11). The neurovegetative symptoms and psychomotor symptoms of melancholia, considered cardinal features, were the first to improve. Some studies have reported improvement of these symptoms after stimulation of bottom brain structure, such as the diencephalon. Limbic and cortico-subcortical networks would be related to the mood, motor, and psychotic symptoms (Parker and Hadzi-Pavlovic, 1996; Fusar-Poli *et al*., 2011).

In almost all ECT sessions she experienced motor and EEG seizures. Although the exact mechanisms of action of ECT are not known, it is considered that convulsions represent good stimulation parameters that induce neural plasticity, neurogenesis, and treat abnormal brain oscillations, which to some extent can resemble abnormal brain oscillations evoked in laboratory (Silva-dos-Santos, 2017). The induced seizures caused by the stimulation can propagate in a wave-like manner and eliminate such abnormal oscillations. This can occur in a top down, diffuse pattern, and/or bottom-up direction. Regardless of the direction of the electrical stimulus or the seizure wave-like propagation, we hypothesize that the amelioration of symptoms occurs, preferentially, from the reptilian to the mammalian and finally to the neomammalian brain (see Supporting Content 8), according to a phylogenetic viewpoint (Figure 11).

Contrary to some recent brain stimulation methods, in which closed loops are applied to record and stimulate the brain multiple times per session (Pais-Vieira *et al*., 2016), usually each ECT session has a limited number of stimulations. It remains to be clarified whether or not a closed loop brain stimulation system would rapidly treat a patient's symptoms or if, due to the bottom-up sequence of clinical improvement, it would require some time (days/weeks) to allow medium-long term neuroplasticity to occur.

Insomnia	Appetite loss	Motoric manifestations	Depressed mood	Delusions
Brain stem	Hypothalamus	Subcortical Low level	Subcortical	Subcortical
Reticular activating system		Middle level High level	Limbic system	Basal ganglia
Hypothalamus		Cortical	Neocortex/frontal	Neocortex/frontal

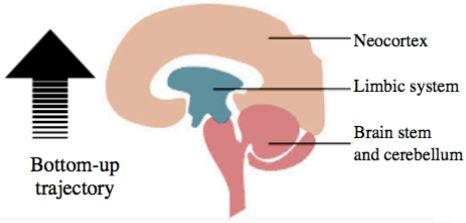


Figure 12. Major brain functions and their corresponding neuroanatomical areas (left). The proposed bottom-up trajectory of symptom improvement (right).

Note: Adapted from Silva-dos-Santos, A., Venda, D., Sales, M.B., Velho, M.V., Gracias, M.J. (2021): 'Bottom-up neuroanatomical pattern of symptom remission in melancholic depression after electroconvulsive therapy: a case report and literature review', *Psychogeriatrics*, [online] Volume 21(2): 252-254. Reproduced with permission of the publisher.

4.3 Symptomatic improvement of acute mania associated with a single session of electroconvulsive therapy: a proposed concept of neuroversion

4.3.1 Key Message

A single ECT session, consisting of 3 trials, was associated with remission from an acute mania episode, despite no evoked seizures. Here, we compare this phenomenon to the well-known procedure of cardioversion. We name it *neuroversion* – normalisation of brain activity triggered by one electrical stimulation session.

4.3.2 Learning points

— A serendipitous clinical case is presented: a single ECT session was associated with symptoms remission;

— The term neuroversion is introduced, and compared to cardioversion, as a possible mechanism to normalise brain function;

— Electroencephalographical activity in acute mania, as well as the effect of ECT on brain function, are highlighted.

4.3.3 Case presentation

A 63-year-old woman, followed at our psychiatric outpatient clinic for Bipolar Disorder type I and intellectual disability (DSM-5), was admitted to our inpatient unit due to a three-day episode of psychomotor agitation, elevated mood, decreased need for sleep, accelerated speech, and persecutory delusions. She was not compliant with her psychiatric medication. There were no relevant laboratory findings, and the urine toxicology was negative.

The patient's past medical history included acute myocardial infarction and chronic kidney disease (single functional kidney). Upon admission, her main comorbidities were arterial hypertension, auricular fibrillation, type 2 diabetes, and pernicious anaemia (under vitamin B12 replacement therapy). Her initial psychiatric medications were quetiapine (100 mg), haloperidol (5 mg), and valproic acid (500 mg). On the ninth day of hospitalisation, she had a sudden bradycardia episode, associated with altered consciousness and generalised hypotonia. The laboratory work-up was unremarkable and brain computerised axial tomography excluded pathological findings. However, the electrocardiogram (EKG) showed atrial fibrillation with a controlled ventricular response. The medical staff admitted the diagnosis of bradycardia secondary to psychiatric medications, whose dosages were reduced. In this context, ECT was a safer therapeutic option and was initiated after obtaining the patient's informed

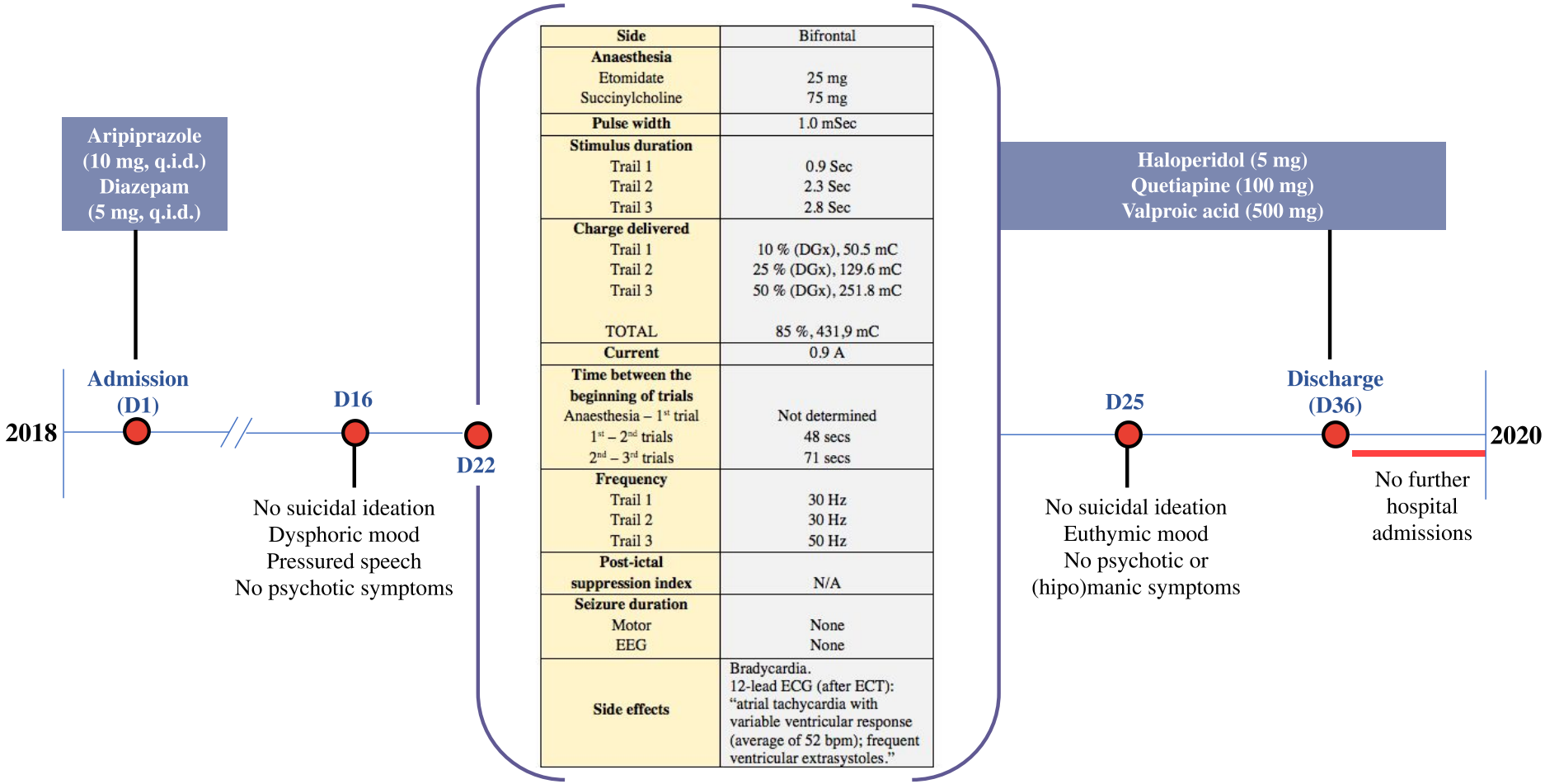
consent. The anaesthesia protocol details and the ECT electric parameters are shown in Topic S1 (Supporting Information).

The ECT session was comprised of three consecutive trials (charge 10%, 25%, and 50%) since dosage titration is required in the first session. We did not start with a charge corresponding to half of the patient's age. Instead, we started low and went slow. Time intervals between each trial are shown in Figure 1. There were no seizures (neither motor nor electroencephalographic) during the stimulation and post-stimulation periods.

Surprisingly, the patient became euthymic after leaving the recovery area, with no elated mood, dysphoria or delusions. However, it should be noted that she had an episode of bradycardia in the immediate postictal period, with an average variable ventricular response of 52 beats/min and frequent extrasystoles.

We therefore decided to discontinue ECT for the following reasons: 1) since the patient had an event of post-ECT bradycardia, she would be at an increased risk in further ECT procedures; 2) the patient achieved a remarkable clinical response after the first treatment session. According to the Clinical Manual of Electroconvulsive Therapy, which is in line with the most recent evidence, «no set number of treatments is required to complete a full course of ECT» and, «as soon as the patient is judged to have achieved a maximum clinical response, the ECT course is terminated» (for further details see the Introduction of Supporting Information). On this basis, the patient continued oral pharmacological therapy with a mood stabiliser and an antipsychotic (Figure 12). Her behaviour was monitored closely to rule out transient or spontaneous symptomatic improvement.

Having remained asymptomatic, she was discharged 15 days later. No further ECT was needed since she remained euthymic. A long-acting injectable antipsychotic was considered to address the patient's nonadherence to oral medications. However, due to her age (almost 65 years) and her past cardiovascular history, she was discharged on the same oral combination regimen.



Side	Bifrontal
Anaesthesia	
Etomidate	25 mg
Succinylcholine	75 mg
Pulse width	1.0 mSec
Stimulus duration	
Trail 1	0.9 Sec
Trail 2	2.3 Sec
Trail 3	2.8 Sec
Charge delivered	
Trail 1	10 % (DGx), 50.5 mC
Trail 2	25 % (DGx), 129.6 mC
Trail 3	50 % (DGx), 251.8 mC
TOTAL	85 %, 431,9 mC
Current	0.9 A
Time between the beginning of trials	
Anaesthesia – 1st trial	Not determined
1st – 2nd trials	48 secs
2nd – 3rd trials	71 secs
Frequency	
Trail 1	30 Hz
Trail 2	30 Hz
Trail 3	50 Hz
Post-ictal suppression index	N/A
Seizure duration	
Motor	None
EEG	None
Side effects	Bradycardia. 12-lead ECG (after ECT): "atrial tachycardia with variable ventricular response (average of 52 bpm); frequent ventricular extrasystoles."

Figure 12. A schematic timeline of the patient's reported hospitalisation, including the main clinical features and the detailed ECT treatment protocol.

Note. From Silva-Dos-Santos, A., Sales, M.B., Venda, D. (2021): 'Symptomatic improvement of acute mania associated with a single session of electroconvulsive therapy: a proposed concept of neuroversion', *Bipolar Disorders*, [online] Ahead of print. Reproduced with permission of the publisher.

4.3.4 Discussion

The first-line treatments for acute mania are lithium, antiepileptic mood-stabilisers, and antipsychotic drugs. ECT is reserved for drug-resistant patients, although it is the first-line treatment for severe or delirious mania with life-threatening physical exhaustion.

Contrary to depression, there is a lack of prospective, randomised studies on the use of ECT for acute mania. The literature documents high rates of response and remission, even in drug-resistant patients. However, its electrophysiological and molecular pathways are poorly understood.

Our patient was first treated with antipsychotics and a mood stabiliser. Initially, we did not consider ECT as a treatment option for the manic episode. However, by serendipity, we had to choose this therapeutic approach. First, she had an episode of bradycardia on the ninth day after admission. Since no physical cause for the bradycardia episode was identified, we assumed it was secondary to the psychotropic medication. Hence, the patient was treated with ECT as an add-on to the medication. She underwent one single session. Surprisingly, another serendipitous event prevented further sessions – she had a new episode of bradycardia immediately after the procedure while in the post-ECT recovery room. We suspended the ECT treatment and resumed the pharmacotherapy approach. Unexpectedly, her symptoms improvement was associated with a single ECT session. Although possible, it is not probable that sudden and sustained improvement would have occurred as part of the natural course of mania, by the effect of psychopharmacological treatment and/or anesthesia, nor due simply to the placebo effect (for further details, see Topic S2).

Although the exact ECT mechanisms of action remain unknown, seizure activity is required to trigger a response[2]. According to the literature, a few ECT sessions are needed to reach symptomatic remission in manic, mixed-state, depressive, catatonic, agitation or psychotic episodes. However, in this report, a single ECT session was associated with symptoms remission, and the patient did not experience seizure activity (neither motor nor electroencephalographic) during the procedure.

We hypothesise that our patient's improved response was associated with an electrophysiological *forced normalisation* phenomenon comparable to the cardioversion procedure frequently used in cardiology to treat cardiac arrhythmias (such as atrial fibrillation).

Forced normalisation (FN) is a classic phenomenon, first described by Landolt in 1953. Formally, this concept evolved to designate the emergence of psychiatric or behavioural disturbances following the abolition or reduction of epileptic activity (normalisation of EEG), usually after treatment modalities such as anticonvulsant medications, temporal lobe surgery or vagal nerve stimulation[3]. The exact underpinning mechanisms of the interplay between psychosis and epilepsy remain unknown and are not within this manuscript's scope. However, we highlight that we use the intuitive electroencephalographic meaning of this term (normalisation of EEG) and disregard their inherent clinical aspects. Applying this notion to the present case, first, we looked at the patient's EEG tracing. Its visual inspection showed an irregular baseline with high-frequency brain waves (Figure 13), different from a regular EEG seen in euthymic patients (see Topic S3). A parallel can be drawn here, in a broad sense: from the neurophysiological and psychiatric viewpoints, the baseline might be

conceptualised as a neuronal arrhythmia, in the way that auricular fibrillation is a cardiac arrhythmia (as illustrated in Figure 13).

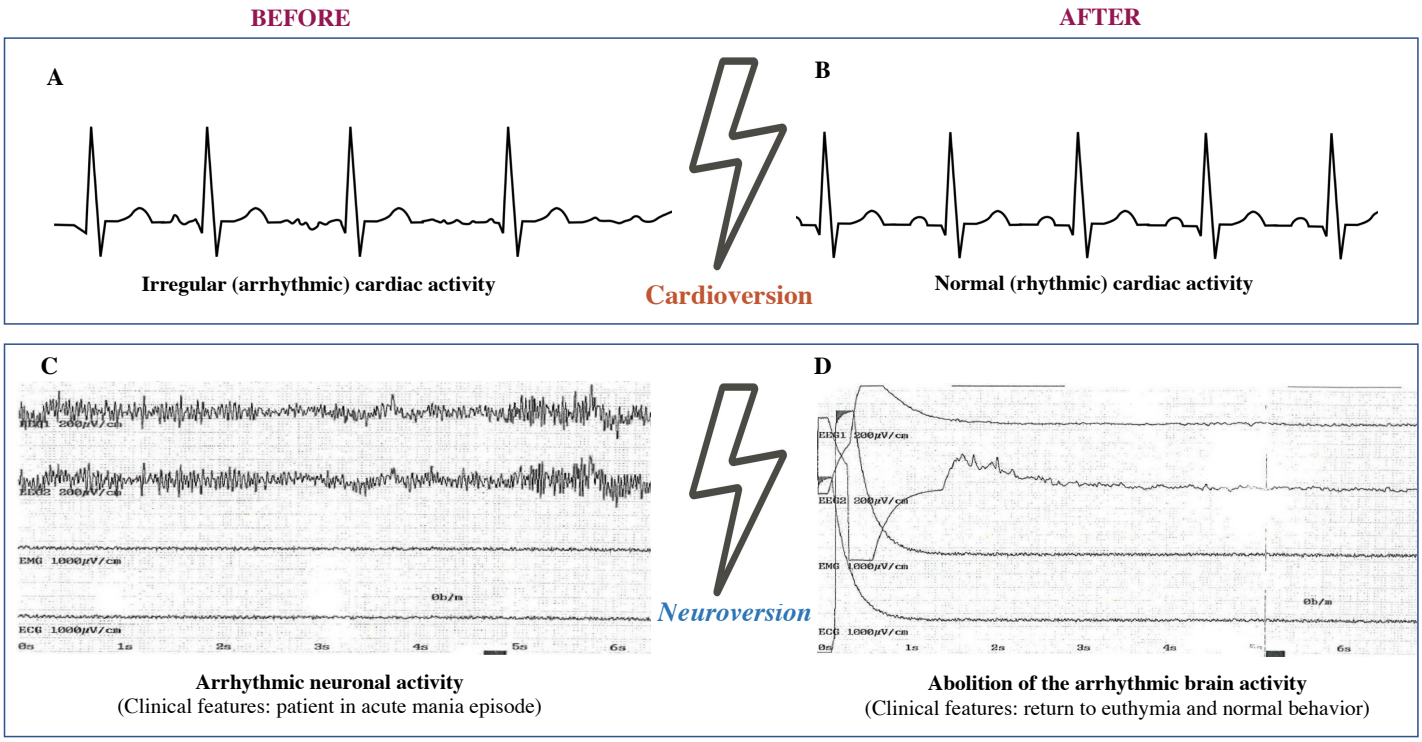


Figure 13. Schematic representation of the proposed parallelism between cardioversion and neuroversion. A | EKG showing atrial fibrillation. B | Normal sinus rhythm following cardioversion. C | The patient's baseline EEG record before anesthesia. Note an irregular baseline with high frequency and high amplitude brain waves, suggesting possible arrhythmic neuronal activity during an acute manic episode. D | The patient's EEG record after an ECT trial. Note the absence of seizure activity in the post-stimulation period. EKG, electrocardiogram. EEG, electroencephalogram.

Note. From Silva-Dos-Santos, A., Sales, M.B., Venda, D. (2021): 'Symptomatic improvement of acute mania associated with a single session of electroconvulsive therapy: a proposed concept of neuroversion', Bipolar Disorders, [online] Ahead of print. Reproduced with permission of the publisher.

We do not want to raise any heresy. Instead, we intend to be on the shoulders of the giants of psychiatry. We humbly interpret our serendipitous findings as a putative mechanism of an electrophysiological forced normalisation and call it *neuroversion*. Though such term was previously used by Williams et al., herein we suggest a somewhat different meaning, in the line of established concepts such as resetting, reboot or restart. We do not know its possible neural mechanisms, but we raise the hypothesis that it might resemble the cardioversion's electrophysiology. Alternatively, it might be similar, at least in part, to the mechanism throughout some neural stimulation methods, such as spinal cord stimulation, ameliorate epilepsy.

Chapter 5

Conclusion

Geriatric patients with severe and/or treatment-resistant mood disorders occupy a considerable portion of all ECT recipients at HVFX. Irrespective of age, major depression (either in the context of unipolar or bipolar disorders) was the most common indication criteria for referral, a finding that is consistent with the overall picture of Western countries. The outcome results were particularly impressive, and the vast majority of the study population attained symptomatic remission. This study provides real-world evidence that lends further support to the remarkable effectiveness and speed of action of ECT, both as a rescue or emergency life-saving intervention and an add-on treatment on the journey to remission and functional recovery.

These findings also confirm that, in light of current best practice, there is no scientific reason to fear ECT, providing that both patients and clinicians are well informed. This procedure revealed an excellent safety profile for younger and elderly patients alike, even among individuals at high risk of adverse effects (including elderly patients and those with comorbid neurological or cardiac diseases). Together, the present data concur to demonstrate that, for many patients, the benefits of providing ECT will far outweigh the inherent risks, and that there is a high price to pay for simply discarding ECT from the arsenal of therapeutic options. As a corollary to the above, this study strongly argues for the use of ECT early on in the treatment of the most severely ill patients. This recommendation takes a special place among geriatric patients who either do not tolerate or do not adequately respond to treatment as usual.

In an apparent paradox, the proportion of ECT-treated inpatients in the psychiatric unit of HVFX stands at the lower end of European countries represented in the medical literature, yet being substantially higher than the percentage found in existing national data. This study, therefore, provides a basis to conclude that ECT is being underused in Portuguese mental health services. Even in facilities equipped with ECT wherein there is readiness of practitioners to prescribe and/or apply ECT, and readiness of patients to accept it, access to treatment is jeopardised by nongeographical and nonclinical factors. This entails that an unknown number of Portuguese patients do not have access to a treatment capable of altering the course of severe psychiatric conditions. In the studied unit, three major barriers to ECT provision are currently at play (and implicitly linked): insufficient availability of anaesthesiologists; limitations of space; and negative attitudes by patients and health care professionals toward ECT. The role of other bureaucratic or political factors remains unclear.

The present study is meant as a plea for further attention toward the use and practice of ECT in Portugal. A pressing goal for the mental health workforce should be to conduct a systematic evaluation of patient-level data covering all aspects related to ECT. Local barriers to access and unmet needs must be mapped to a national extent, so as to better assess the real treatment gap in each region. Eventually, mental health policies and collaborative efforts with the bodies in charge of healthcare planning will be required to fully integrate ECT into real-world clinical practice and to support equitable access for whom it is indicated. It is my hope that the output data presented here may be a helpful contribution to inform future studies and, ultimately, to make ECT a priority in its own right, within patients' reach.

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